SIMULATION-BASED DECISION SUPPORT SYSTEM FOR CELL THERAPY MANUFACTURING AND SUPPLY CHAIN

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SIMULATION-BASED DECISION SUPPORT SYSTEM FOR CELL THERAPY MANUFACTURING AND SUPPLY CHAIN

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Declare the past, diagnose the present, foretell the future.
— Hippocrates

For my wife June and my son Louis

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LIST OF SYMBOLS AND ABBREVIATIONS

AI	Artificial Intelligence
AlloCT	Allogeneic Cell Therapy
APF	Academic Production Facilities
AuCT	Autologous Cell Therapy
BCPS	Bio-Cyber-Physical System
CAR-T	Chimeric Antigen Receptor T Cells
CFR	Code of Federal Regulation
cGMP	Current Good Manufacturing Practice
CGT	Cell and Gene Therapy
CGTP	Current Good Tissue Practice
COGS	Cost of Goods
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
DSS	Decision Support System
EOQ	Economic Order Quantity
FDA	Food and Drug Administration
FDA	Food and Drug Administration
FIFO	First In First Out
IPF	Industrial Production Facilities
iPSC	Induced Pluripotent Stem Cells
KPI	Key Performance Indicator
M & SC	Manufacturing and Supply Chain

mAb	Monoclonal Antibodies
MSC	Mesenchymal Stem/Stromal Cells
PBS	Phosphate-buffered Saline
PQ	Priority Queueing
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Check
QTPP	Quality Target Product Profile
R & D	Research and Development
RL	Reinforcement Learning

SUMMARY

Cell therapy is an emerging field in regenerative medicine that uses living cells to treat disease. The potential therapeutic benefit of cell therapy is creating a rapidly growing industry estimated to be a $55 billion global market by 2024. However, meeting this massive demand requires the development of novel tools and technology to solve the unique challenges facing the manufacturing of cell therapy. Compared with traditional biopharmaceutical manufacturing, cell therapy product manufacturing is considerably more challenging due to the greater complexity of working with living cell products. As a result, the cost of cell therapies remains unattainable for most patients, with a long lead time and low production capacity.

This Ph.D. thesis will describe the development and application of an agent-based simulation platform that can create digital representations of a single or multi-network of manufacturing facilities throughout a large region. The platform incorporates a customized manufacturing process for autologous products that are customized per patient, as well as a batch manufacturing process for allogeneic products. A set of case studies will be presented in the thesis to demonstrate how the platform enables manufacturers to devise system-level decisions to improve facility design, plan "what if" scenarios for unexpected disruptions, and address an unmet need for reducing costs, increasing speed, and improving yields for cell therapy production and distribution.

CHAPTER 1 INTRODUCTION

1.1 Background

Cell therapy is an emerging therapeutic method that uses a patient's own cellular material to treat disease. Cell therapy has received regulatory approval for a small number of blood cancers (June, O'Connor, Kawalekar, Ghassemi, & Milone, 2018; Rosenberg & Restifo, 2015), and shown promising results in clinical trials for a number of other indications including blood disorders (Ribeil et al., 2017; Thompson et al., 2018), and autoimmune diseases (Ellebrecht et al., 2016; Miyara, Ito, & Sakaguchi, 2014). The transition from clinical trials to commercial products is evolving rapidly because of its tremendous potential benefits for patients. There are currently 1,085 companies developing cell therapies worldwide, with a total of 1,220 clinical trials as of the end of 2020 (Lambert, 2021).

Based on the origin of the cellular material, cell therapy can be categorized into autologous cell therapy (AuCT), where the patient's own cells are used, or allogeneic cell therapy (AlCT), where the cellular material comes from a healthy donor. The use of autologous cells can significantly reduce the risk of immune rejection and disease transmission (Kazmi, Inglefield, & Lewis, 2009), but at the cost of increasing the complexity of the manufacturing and supply chain process. As the AuCT product is patient-specific, a separate batch of cells is manufactured for each patient. A typical manufacturing process for AuCT starts by taking a cell sample from the patient in the clinic, then transporting these cells to a central manufacturing facility for manipulation. At the manufacturing facility, these cells undergo isolation, purification, expansion, harvest, and

formulation. For a genetically modified cell product such as chimeric antigen receptor t-cells (CAR T-Cell), the cells will also undergo activation and gene delivery through viral transduction or electroporation before expansion. After formulation, these cells are tested and then released back to the clinic for administration to the same donor patient (Bartel, 2015; Levine, Miskin, Wonnacott, & Keir, 2017).

Unlike the scalable allogeneic therapies, which can be modeled after therapeutic monoclonal antibodies (mAbs) production with established business models and robust supply chains, ideal manufacturing and distribution approaches have not yet been fully determined for AuCT. Many current manufacturing facilities for autologous therapies are designed or tuned to deliver innovative products that will be used in carefully controlled clinical trials. Notably, the facilities that are affiliated with universities or research centers usually have responsibilities other than manufacturing autologous therapies. For example, it is quite common that a production facility of an academic medical center supports several different clinical trials, including investigator-initiated trials. These “academic production facilities” (APFs) have the flexibility to reconfigure manufacturing space to produce different types of cell products. However, a significant challenge is responding to changes with real-time information in industrial production scenarios. Everything in every process, including machine schedules, personnel allocations, and reagent usage, is scheduled significantly before the actual production starts. Pre-deployment planning is a strategy that helps accomplish multiple types of tasks on time, rather than an efficient, low-cost, consistent strategy for accomplishing the same type of task. Considering that AuCT is an entirely patient-specific product, and the patient's condition is likely to change at any time,

this strategy, which relies on pre-planned production and distribution, is even less flexible in an industry setting.

The few companies that so far produce FDA-approved commercial AuCT products, such as Novartis Pharmaceuticals Corporation, Gilead Sciences, and Dendreon, utilize their own dedicated manufacturing facilities. Unlike APFs, where different types of products keep the production process open for adjustment at any time, these "industrial production facilities" (IPFs) need to optimize the production process for a single or several similar products. At a much larger manufacturing scale, IPFs also need to develop a sophisticated supply chain network that can ensure reliable and on-time deliveries to treatment facilities across the country or the globe. In addition, the difficulty of many operational aspects in AuCT production facilities drastically increases with scaling up, such as production scheduling, prioritization, inventory management, and workforce management.

Many unique challenges exist in scaling up AuCT manufacturing as illustrated in Table 1.1. At present, there are not many IPFs for AuCT, and there is thus still much room for exploration on the optimal configuration strategy. This thesis proposes the development of a simulation platform to model cell therapy manufacturing and supply chain to experiment with new configurations to help tackle these challenges.

1.2 Challenges in autologous cell therapy manufacturing

The AuCT supply chain network is composed of manufacturing facilities, suppliers, clinics, transport of specimens from clinics to facilities, and transport of therapies from facilities to clinics. Each facility is comprised of bioreactors (the manufacturing capacity), AuCT orders assigned to the facility, reagent and supply inventory, and the skilled

workforce. Scheduling and coordinating patients with spare production capacity at the manufacturing facility within the product shelf life can significantly increase the complexity for scaling out commercial production. As the production ramps up to meet national or even global demand, manufacturers must choose between a centralized or more decentralized manufacturing network to determine the optimal number and locations of the manufacturing facilities, as well as the functions and operations conducted at each facility (Harrison, Rafiq, & Medcalf, 2018). A simulation platform could be a valuable support tool to understand how these decisions will affect the manufacturing capacity, which in turn affects the cost of these cell products. In addition, a simulation platform could be used to study how delays affect the quality of the cells and optimize the scheduling of these manufacturing and quality testing steps.

There is a need for real-time and efficient communication between clinics, manufacturers, and reagent suppliers. Real-time interaction between the manufacturing facility and the healthcare staff will allow better prediction of product delivery date based on the current manufacturing capacity. For example, if a patient's condition suddenly becomes unsuitable for AuCT, the clinic should immediately notify the manufacturer to cancel subsequent production to reduce the loss in terms of cost and manufacturing capacity, and the cancellation of this order may also result in subsequent changes in reagent requirements. Similarly, if the reagent supplier foresees a disruption, the manufacturer should be notified immediately to take appropriate action, which in turn will cause the clinic to adjust the patient's AuCT injection schedule. The complexity of interaction between parties in the AuCT supply chain network exceeds the interactions in supply chain networks of other existing industries. While no analytic tool is available to address the

complexity at this high level, it is feasible to capture this complex interaction using a multiscale simulation with built-in stochastic algorithms.

Currently, the critical reagents in the manufacturing process of AuCT rely on only a few or, in many cases, the high-risk situation of a single supplier. Other high-risk situations include a reagent supply disruption, which could result in reagent shortages or stock-outs in all IPFs, significantly reducing yield and hence significantly reducing patient benefit. A simulation platform could assist in the evaluation of "what if" scenarios and the preparation of risk mitigation strategies. The efficiency and cost of deploying any risk mitigation strategy can also be estimated by running computational experiments on the supply chain simulation.

According to the Regenerative Medicine Standards Landscape, there are over 60 existing standards that are relevant for the cell therapy process (Nexight Group & Standards Coordinating Body, 2018). However, many of these relevant standards lack a sufficiently specific or useful guide for AuCT commercial development. The lack of standards can create significant difficulties in converting the clinical trial manufacturing process into a full-scale commercial manufacturing process (National Academies, 2017). A simulation platform for planning AuCT production will need to be flexible and have a high degree of freedom to allow the manufacturer to explore the impact of different standards on their manufacturing process. Such platform can support a policymaker with information including how a policy affects the efficiency and the robustness of the supply chain.

Table 1.1 A list of challenges that differentiate AuCT manufacturing from conventional manufacturing problems

Unique Challenges in Scaling AuCT Manufacturing
• Time-dependent product quality that is hard to predict
• Large patient-to-patient variability in the starting material that propagates to the final cell product
• Lack of standards and industrial understanding to choose appropriate reagents, materials, and equipment for large scale commercial manufacturing that is FDA-compliant
• Rapidly changing patient condition and disease progression
• A complex logistic network that extends beyond manufacturing facilities
• Vulnerable to supply disruption due to single sourcing for most materials

1.3 Emerging allogeneic cell therapy manufacturing

Unlike the autologous approach, an allogeneic process does not require the collection of specimens from the patient receiving the therapy. This difference affects inbound logistics, manufacturing, and distribution in important ways. The raw material collection and manufacturing processes are decoupled from one another, as are the manufacturing and drug product distribution processes. The former processes are separated by a buffering step – all outputs of the manufacturing process are cryopreserved for inventory, with fulfillment originating from said inventory as needed.

As starting materials are donor- rather than patient-derived, manufacturing is not initiated by real-time requests, with apheresis conducted in line with availability at a manufacturing site. Products are manufactured in campaigns, which are planned to meet

the demand for stock and demand fulfillment. Resources can be procured and staged to meet the needs of the specific campaign, therefore leading to a less time-dependent scheduling process than is common in the production of autologous therapies. In this way, AlloCT resembles conventional small molecule or biologics supply chains.

While both autologous and allogeneic processes share most of the same unit operations and thereby present a similar degree of complexity, allogeneic production allows for production campaigns of lot size that spread time and cost across hundreds of doses. Furthermore, the ability to manufacture on the basis of donor material – with healthy donors being selected, screened, and subjected to extensive testing – and then to cryopreserve doses, enables a more comprehensive approach to quality control and a more timely delivery, as the leukapheresis and outbound logistics are eliminated as gating steps in the process.

Indeed, the ability to decouple the cell therapy from the patient has become a new frontier in this rapidly evolving space. Moreover, while questions remain regarding the therapeutic equivalency between autologous and allogeneic products, the need to reduce costs and increase economies of scale through standardization and process automation will continue to drive efforts to create effective allogeneic therapies. Some therapeutic candidates have begun to generate positive clinical results (Mailankody et al., 2020; Sommer et al., 2019), with more anticipated in the near future.

The transition to an allogeneic approach to CAR-T will certainly depend on therapeutic efficacy. However, it will also depend on cost. To date, efforts to map the costs associated with manufacturing and delivering CAR-T therapies have been limited, especially emerging allogeneic therapies.

1.4 Existing studies on cell therapy modeling

Currently, there exist a few studies on analytic or empirical modeling for the cost of cell therapy manufacturing (Abou-El-Enein et al., 2013; Harrison, Rafiq, et al., 2018; Harrison, Zylberberg, Ellison, & Levine, 2019; M. J. Jenkins & Farid, 2018; Lopes, Sinclair, & Frohlich, 2018; McCollister et al., 2018; Simaria et al., 2013). Although these studies provide valuable information regarding the economics of the cell manufacturing process, none of them provide the information detailed enough to address issues specific to a single cell therapy facility, let alone the interactions between multiple facilities and different stakeholders. A simulation-based tool may serve better than oversimplified models in most decision-making scenarios. However, no such simulation tool can be found in the current body of literature. As a result, the development of a three-level (clinics, manufacturing facilities, and suppliers), two-scale (facility and supply chain network), stochastic simulation model is described in this thesis. This model may be used as a decision support system (DSS) for the cell therapy supply chain in service to manufacturers, health care providers, and ultimately patients.

1.5 Aims and organization of the thesis

This thesis will describe a simulation-based decision support platform to help cell therapy manufacturers improve production and distribution by reducing lead time, failure rate, and production costs. The simulations help manufacturers identify problems early on and throughout the overall manufacturing and supply chain, and could lead to reduced costs, improved yield, quality, and speed for the regenerative medicine products. Simulation case studies for different cell types (CAR-T, MSC, and iPSC) and cell sources (autologous and allogeneic) are developed to test the validity of the platform. Case studies that inform

decision-making in cost reduction, automation, logistics, inventory management, risk management, and scheduling are presented to test the functionality of the platform (Figure 1.1).

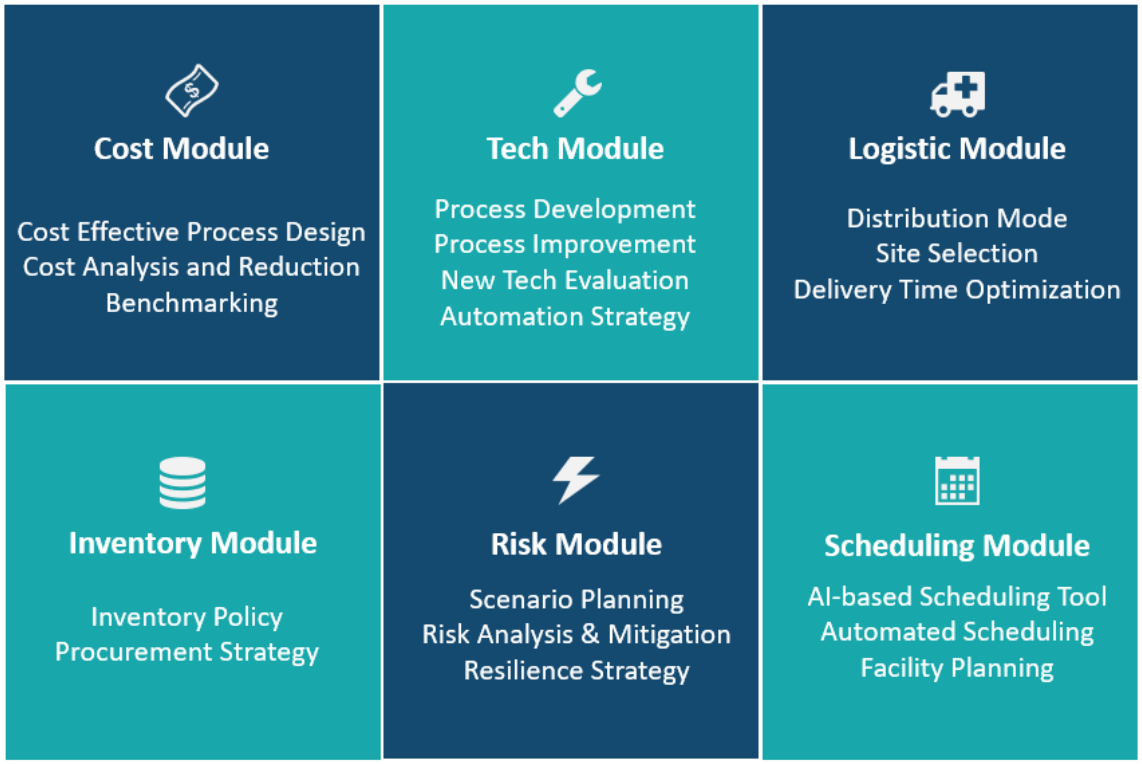

Figure 1.1 Functional modules of the simulation-based decision support platform

The thesis is organized as follows: **Chapter 2** describes the development and features of an agent-based simulation platform for autologous cell therapy manufacturing using the production of autologous CAR-T for cancer treatment as a case study. The chapter also describes how the platform can be used to identify bottlenecks in production and design computational experiments to improve the process to reduce cost and lead time.

Chapter 3 describes the development of a decisional support tool for cost-effective bioprocess design for cell therapy. The chapter will establish a framework for conducting cost analysis for the cell therapy industry, investigate the cost structure of current products and potential areas for cost reduction, as well as provide a detailed case study on a cost-effective design of an allogeneic mesenchymal stem cell (MSC) manufacturing facility for joint cartilage damage.

Chapter 4 provides a detailed case study describing how the decisional support tool can be used to produce a cost-effective design of a commercial manufacturing facility for the production of a cell therapy product containing human mesenchymal stem cells (MSCs) for the treatment of joint cartilage defects.

Chapter 5 investigates the impact of supply chain and labor disruption on cell therapy manufacturing performance and evaluates alternative scheduling policies to improve patient outcomes using the developed simulation platform. The platform will simulate different disruption and shortages scenarios during the COVID-19 pandemic (Fauci, Lane, & Redfield, 2020) and provide decision support on how manufacturers can build resilience to mitigate the impact of disruptions.

Chapter 5 summarizes the conclusions from this thesis and discusses some ongoing and future works to improve the decision support system and extend the application of the system to new possible avenues.

Some results presented in the thesis have already been published and presented in academic journals and conferences. Parts of the thesis are adapted from manuscripts that are published, submitted, or in preparation (Liu, Tseng, & Lin, 2019; Liu et al., 2021; Wang et al., 2019).

CHAPTER 2 AGENT-BASED SIMULATION MODEL FOR CELL THERAPY MANUFACTURING AND SUPPLY CHAIN

2.1 Digital simulation framework for autologous cell therapy manufacturing

The proposed simulation framework has an array of key features to address the unique challenges expounded in **Chapter 1**. These features include a multiscale structure, multiple key performance indicators (KPIs), stochasticity when appropriate, and a highly customizable framework. These features reflect the very minimal requirements to be able to capture the complexity of the AuCT supply chain problem. Sophisticated functions can be built upon the basic framework to solve specific cases. The design of the computational experiment depends on the specific users' considerations of pinch points in sourcing, production, and delivery.

2.1.1 Multiscale structure

The most fundamental difference between the AuCT supply chain problem and conventional supply chain problems is that the AuCT supply chain model must include both the "microscale" activities inside a cell manufacturing facility and the "macroscale" interactions at the supply chain network level. In a conventional supply chain problem, the manufacturing facility and the supply chain network can be modeled separately since the products produced in the manufacturing facilities are interchangeable. Therefore, the manufacturing nodes in a conventional supply chain network model can be treated as "black boxes" where the detailed manufacturing procedures can be modeled with a separated simulation. However, in the AuCT supply chain problem, each product is linked with an individual patient. It is a truly build-to-order (BTO) supply chain for a bespoke

product. The patient's condition can influence the timing of production and quality control procedures. Moreover, the patient is not only the consumer of the product but also the supplier of the raw material. If the manufacturing process of any product fails due to any reason, a request for a new specimen may be issued from the manufacturing facility to the clinic. Therefore, in a simulation run, it is essential to ensure real-time communication between the manufacturing facility level and the supply chain level, which requires the model to contain both the micro and the macro scales.

2.1.2 Microscale simulation

The microscale simulation reflects any activities inside a manufacturing facility. The primary subsystems in a cell manufacturing facility include manufacturing procedures (Figure 2.1a), quality control procedures, inventory management, and resource management. Figure 2.1b shows the interface of the microscale simulation platform. The specimens from clinics arrive at the top-left corner and go through the acceptance check and the upstream processing. Then the specimens enter a queue, waiting for bioreactors, operators, and reagents to be assigned by the resource management subsystem. After the necessary resources are allocated, the specimens come to the expansion stage, where several quality control tests will be performed at different time points over the entire course. After the expansion, the products go through the downstream processing and release check subsequently. Qualified products are packed and distributed to the clinics for administration, which can be the same or different clinics from the ones where the specimens were collected. If the product fails any of the acceptance check, quality control tests, or the release check, the facility may request a new specimen to be sent from the patient. If the patient becomes unsuitable for treatment, a signal will be triggered and

abort/pause the corresponding manufacturing process. The inventory management subsystem governs the replenishment of reagents and supplies.

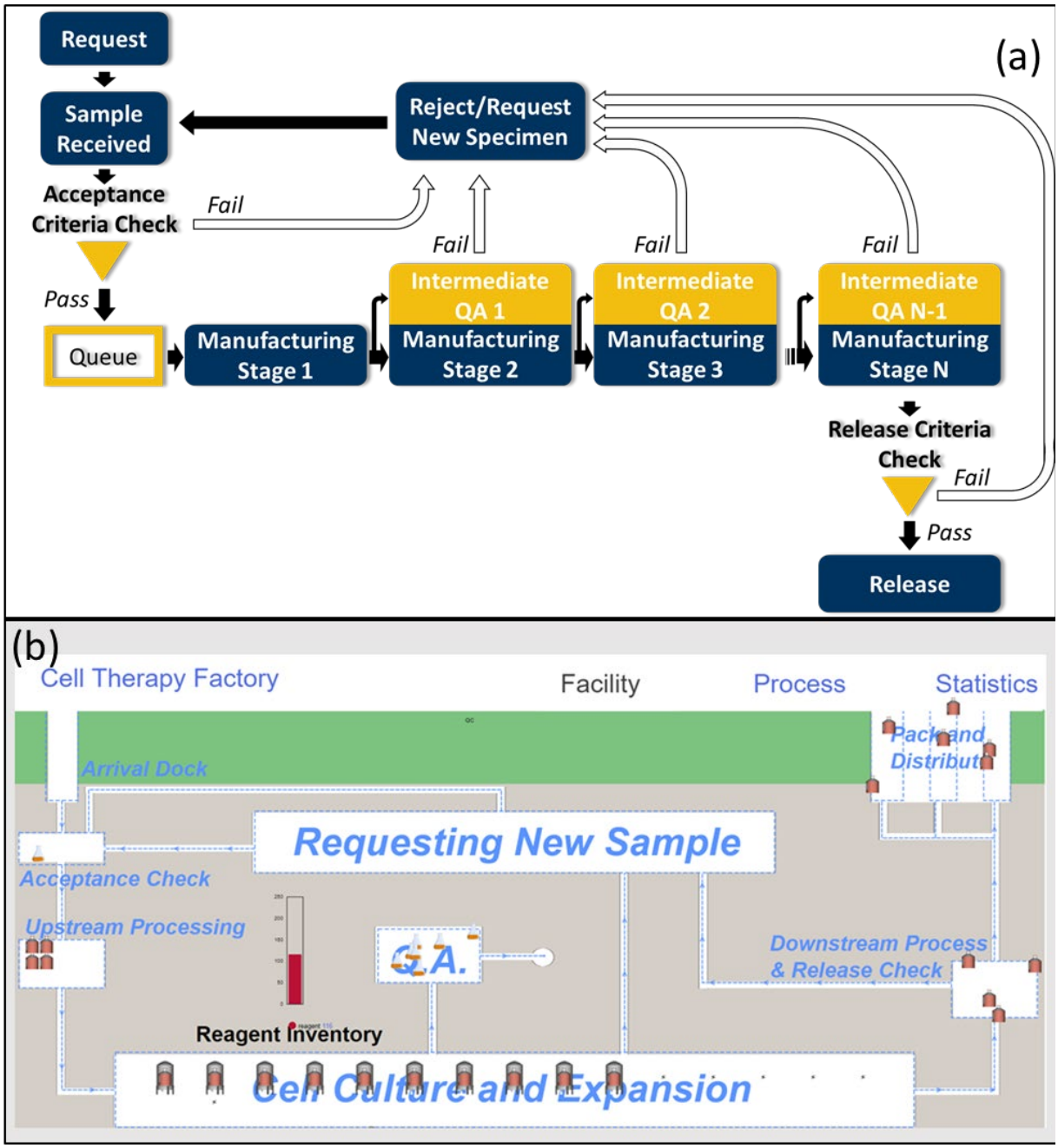

Figure 2.1 The flow chart of activities inside a typical AuCT manufacturing facility; (b) The simulation interface that monitors the internal activities of an AuCT manufacturing facility

Many communication ports exist at various components in this facility to ensure timely interactions with events at the macroscale level. The primary inlet port is at the arrival dock, where the requests and specimens sent from clinic nodes are accepted. The primary outlet port is at the pack and distribution dock, where the products are sent back to the requesting clinics. Every specimen in the facility also has a categorical variable, "Patient Status," that links to the status of the patient. The framework handles a variety of specimens with patient categories using different actions regarding their manufacturing process. The modeling framework (AuCT-Sim) models real-time patients' status changes using a state transition dynamic mechanism with a Markovian property. This structure assumes that patients' state changes are mutually independent, and patients would transit to states that are highly correlated with their health status. In this way, AuCT-Sim simulates real-time changes of patients whose specimens have arrived in the facility for production uses.

Beyond the dynamic of "Patient Status," AuCT-Sim also models the dynamic of specimen quality. Each specimen also has its own "Quality Check" categorical variable that may take a value among "Pass," "Fail," and "Pre-certified." Any product that fails a quality check cannot be replaced by another product; a new request for the patient's specimen is necessary whenever the value of this variable changes to 'Fail.' The change happens when a quality control procedure is performed.

Justifications of quality failure in AuCT-Sim rely on a "Quality" index valued as real numbers between 0 and 1, where 1 indicates that the product is in its "perfect" state and 0 indicates the product is totally unusable. The model assumes that the initial quality of the specimen follows a predefined distribution upon its arrival. As a specimen may

deteriorate over time, the “Quality” index of the specimen will decrease at a random speed, where the exact decreasing amount sampled from a distribution is provided by empirical knowledge. This deterioration can be the result of cells failing to expand, or the loss of sterility, viability, and potency during production. For example, whenever the product is exposed to the outer environment (e.g., to take samples for quality control tests or to be transferred from one container to another), there is a small chance that contamination may happen, and hence “Quality” will be set to 0. The probabilities of contamination at each manufacturing and quality control procedure are preset based on empirical data. In any quality control test, the value of “Quality” will be compared against a preset criterion of that test. Once the “Quality” index is lower than required, the value of “Quality Check” changes to “Fail”; otherwise, the “Quality Check” stays the same.

The inventory management subsystem has a communication port that links to supplier nodes in the supply chain network. There can be multiple inventory replenishment policies preprogrammed. The subsystem can switch between different policies based on a certain global event. For example, the reagent suppliers may forecast a supply change. The manufacturing facilities in the affected distribution region may switch to a more conservative reagent replenishment policy.

Similarly, the resource management subsystem can also communicate with events outside of the facility. In a case of demand surge (which may be caused by a new indication approval or reimbursement allowance, for example), the facility may ask the operators to work overtime until more operators are recruited. There are also communication ports at each quality control step, as they could be out-sourced under certain circumstances.

It should be noted that the microscale simulation of a single manufacturing facility can be packaged into a standalone tool. For example, the demand from clinics can be simulated by a Poisson process or extracted from historical data. Similarly, other communication ports can be fed by random number generators or historical data. The standalone manufacturing facility tool could be used to support decision-making at the microscale. Examples of such decisions include:

- What is the bottleneck of the production capacity?
- What is the relationship between manufacturing configurations, batch capacity, and turnaround time?
- How does a manufacturing innovation impact patient benefit?

2.1.3 Macroscale simulation

The macroscale simulation is designed to model the allocation of multiple manufacturing facilities, which can have different configurations at the microscale level, and the connection with clinics and suppliers as a supply chain network. Figure 2.2 shows the three archetypes of the supply chain network designs: the centralized production model, the regional manufacturing hubs model, and the "point of care" production model. There can also be hybrid solutions that use more than one basic design type in different regions or under different situations.

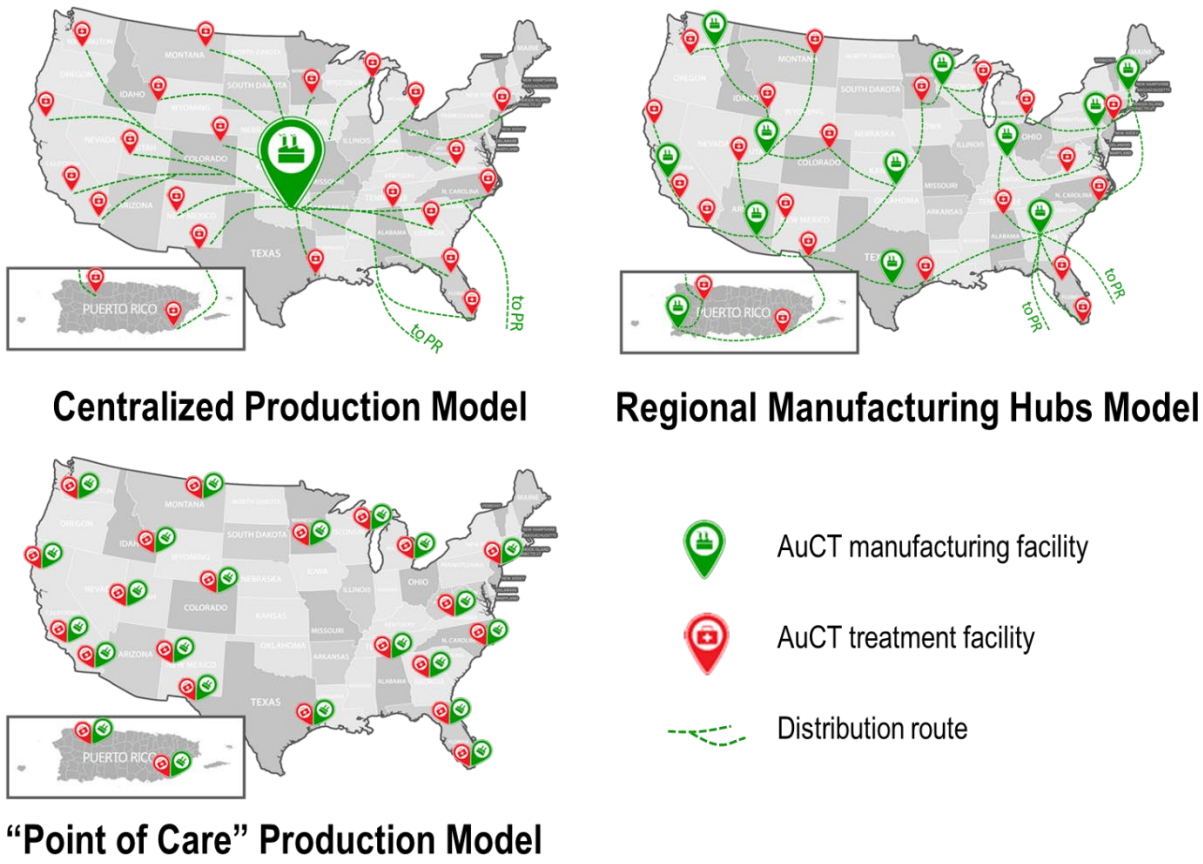

Figure 2.2 Three supply chain network designs

The macroscale simulation for the supply chain can generate valuable information related to the entire AuCT industry or the entire AuCT supply chain network. A few typical questions that could be answered by this tool are listed below:

- What are the strengths and weaknesses of each of the three supply chain network designs?
- What are the optimal number and placement of manufacturing facilities given specific demand distribution over the country or globally?

- What are the risk mitigation strategies to counter an unexpected event, such as a reagent supply disruption, and what are the costs and performance of these strategies?
- How will policies and regulations affect the efficiency and the robustness of the supply network?

2.1.4 Multidimensional key performance indicators (KPIs)

The AuCT-Sim generates and records comprehensive manufacturing and distribution data from each simulation run. The statistical indicators output can be divided into three subgroups: time, efficiency, and cost. Different stakeholders may have different weighting factors assigning to these indicators when evaluating the overall performance.

2.1.4.1 Time-related indicators

The fulfillment time is composed of manufacturing time and distribution time. Each indicates the performance of the manufacturing facility and the supply chain network, respectively. The manufacturing time is the time between when the specimen arrives at the manufacturing facility and when the product leaves the facility for delivery. It can be further divided into four components: processing time, quality control time, queue time, and outage time.

The processing time is the necessary time to produce the AuCT product, including upstream processing, cell expansion, and downstream processing. This component is insensitive to operational decisions.

The quality control time is the time spent on actions to assure the quality of the product, including the acceptance check, the releasing check, and the intermediate quality control assays. The acceptance check and the releasing check are done before and after the

production process. The intermediate quality control steps are distributed at different time points during the production to prevent the risk of wasting resources on continuing processing products that have fallen below the necessary quality requirements. Figure 2.3 shows three strategies to arrange the in-process quality control steps. Based on the relative importance of reducing production time and reducing waste risk, decision-makers can make quality control steps and production steps overlap in time at different degrees. Therefore, the overall quality control time is partially controllable by the manufacturer depending on the configuration.

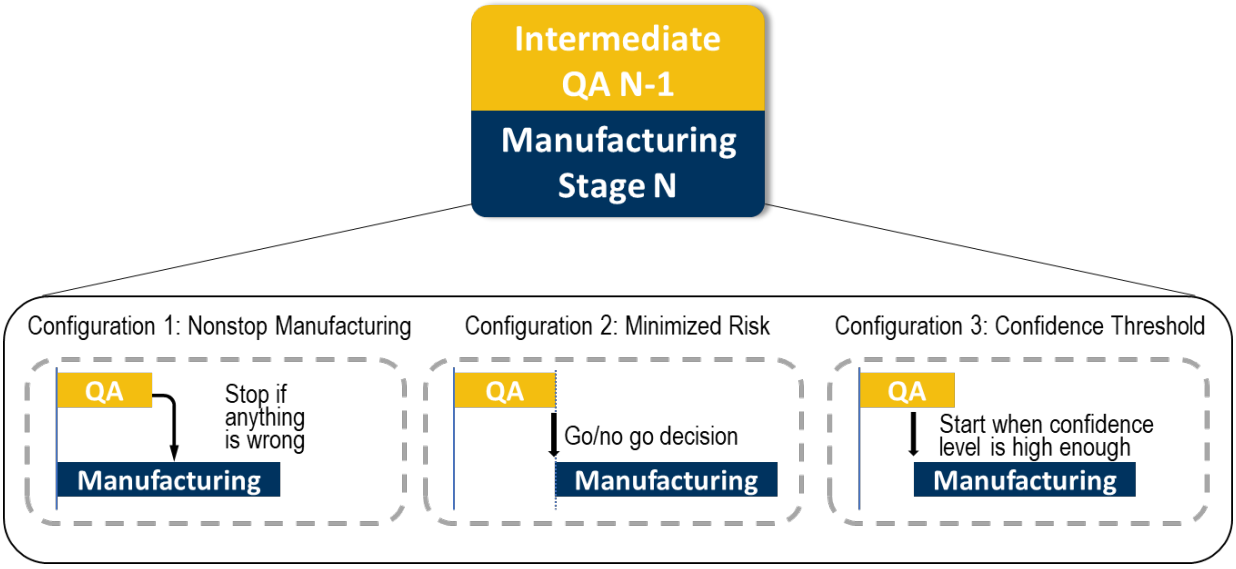

Figure 2.3 Different quality control strategies

The queue time is primarily determined by the demand and the manufacturing capability of the facility. Different queueing policies can also have impacts on the average queue time. The goal of any manufacturing facility should be to make the queue time as short as possible without reducing the utility of resources.

The outage time is the wasted time caused by various unexpected events, such as machine breakdown, power outage, reagent supply disruption. A special case in cell manufacturing is contamination. Any operation involving the interaction of the product and the environment will bring the risk of contamination. The time previously spent on contaminated products is wasted. A new specimen must be requested, and the production must start over.

The distribution time is determined by the design of the supply chain network, which has different aspects including the amount and placement of manufacturing facilities, the methods and routes of delivery, and the real-time conditions of transportation. The goal of optimization is to minimize the distribution time within the constraint of the total cost. Note that the total cost is affected by the cost of transportation and additional factors. For example, the location of a manufacturing facility determines the rent, tax, and salary criteria of its employees. In practice, the location of a manufacturing facility is usually assessed by factors including cost, patient accessibility, the demand distribution.

2.1.4.2 Efficiency-related indicators

The efficiency of the microscale model refers to the utility of machines, reagents, labor, and spaces. Any idle resource implies a fraction of the cost that can be potentially reduced. However, as there is intrinsic uncertainty of the AuCT industry and the product is for therapeutic use, it is necessary to reserve some resources for contingencies. The optimal ratio of reserved resources is difficult to determine solely via the use of the simulation model. Decision-makers can pre-set various scenarios to find the balance between reserved resources and uncertainty handling. Once the balance point is determined, the manufacturer can use the model to find a facility setting that can achieve the desired

utility of different resources. The effects of various disaster scenarios can also be verified using the simulation model.

At the macroscale, efficiency refers to the fulfillment rate of a facility and the marginal utility of a new manufacturing facility at a specified location. Specifically, it measures the increase in the patient benefit, especially patient accessibility, caused by adding a new manufacturing facility. The efficiency of the supply chain network is low if the service areas of many manufacturing facilities substantially overlap.

2.1.4.3 Cost-related indicators

The AuCT-Sim collects cost data for each product during the simulation run and uses the data to calculate two cost indicators: "cost per batch" and "cost per year." Table 2.1 summarizes all indicators that compose the output of the AuCT-Sim. Since different users may have different emphasis on these indicators, the Key Performance Indicator (KPI) is essentially a multidimensional variable with user-assigned weighting factors. The AuCT-Sim's task is to provide comprehensive information for the user to make the decision.

Table 2.1 Key performance indicators calculated by the simulation model

Category	Key Performance Indicator	Relevant Stakeholders							
		Patients	Manufacturers	Healthcare Providers	Researchers	Regulators	Policy Makers	Employees	Reagent Supplier
Time	Fulfillment time	✓	✓	✓	✓	✓	✓		
	> Manufacturing time	✓	✓	✓		✓			
	> > Production time		✓						
	> > Quality control time		✓			✓			
	> > Queue time	✓	✓	✓					
	> > Down time		✓						
	> Distribution time		✓	✓			✓		
Efficiency	Machine utility		✓						
	Labor idle time		✓					✓	
	Reagent reserve		✓						✓
	Unused inventory space		✓						
	Fulfillment rate	✓	✓	✓					
	Increased service coverage	✓	✓				✓		
Cost	Cost per batch	✓	✓	✓			✓		
	Cost per year		✓				✓		

2.1.5 Stochastic settings and highly customizable framework

AuCT-Sim framework can model a large number of stochastic processes in cell manufacturing. These processes include patient demand arrival process, patient health status transition process, specimen viability decay process, cell deterioration/pollution process, production equipment ON-OFF process. All the statistics are highly customizable, which allows the user to modify many parameters before and during each simulation run. These settings may be changed according to the historical data from the specific facility.

Alternatively, the historical data can be used directly as the input with a tabular format. Case studies may also be developed with the AuCT-Sim by modifying various aspects, such as the amount and placement of the clinics, manufacturing facilities, and the reagent suppliers, the route of manufacturing and quality control procedures, the fluctuation in demand and supply, and the quality control thresholds.

The AuCT-Sim may be configured and validated to be a digital representation of an existing facility or a hypothetical facility in a preset scenario. Validation approaches to simulations include subjective expert reviews and objective input-output statistical tests (Sargent, 2013). To assess whether AuCT-Sim produces an equitable or reasonable representation of a manufacturing facility, a three-step validation routine (Naylor & Finger, 1967) may be utilized.

1) Cell manufacturing process experts who are knowledgeable with the system review the validity of this simulation model based on the model animation; this system animation demonstrates manufacturing details, including the production flow from specimen arrival to final shipment, the consuming/replenishing of reagent inventory, the utilizing and releasing of recyclable recourses (bioreactors and technical operators), the failure and repair of bioreactors, and all quality control sampling and testing.
2) Validate model assumptions: All key assumptions must be revealed to review by subject matter experts for a validation check. For assumptions related to input data/distribution(s), implementers should collect related data for statistical tests.
3) Input-output analysis: Output from the system was compared to model outputs with an identical set of input conditions. Given the validated input

parameter(s)/distribution(s), The simulation output should not be significantly different from the physical system output. With data collected from both simulated and physical production systems, the implementers should conduct a nonparametric statistical test to claim the similarity between the two systems. Wilcoxon signed-rank test and Mann-Whitney U tests are two commonly used methods to claim statistical similarity or significant difference.

2.2 Extension to allogeneic cell therapy simulation platform

Based on the AuCT-Sim, an agent-based simulation framework that maps the manufacturing and supply chain process for allogeneic cell therapy manufacturing both at a single facility level and in the context of a larger supply chain network (AlloCT-Sim) was also developed. The simulation framework includes modules for manufacturing process design, quality control procedures, inventory management, and resource management. The agent-based simulation framework provides a good opportunity to track the cost of manufacturing and distributing each product. An industry user can use this function to support operational decision-making, whereas an academic user can evaluate the impact on the cost of any novel technology.

After defining the parameters for the manufacturing system and providing inputs into the simulation framework, users can see simulated results of the operating cost by categories, cost of goods, manufacturing failure rate, estimated final product quality, capacity, and resource utilization during any time of production or other customized performance indices that are of interest to the users. Users can then use these results to aid in decision-making for process design, facility planning, and developing what-if scenarios for any potential disruptions.

2.2.1 Structure of simulation framework

The simulation framework has three components, representing activities at three tiers: suppliers, manufacturers, and clinics. The three components are sourcing and procurement model, manufacturing process model, and distribution model. The first two components are joined by a receiving inventory node, and the last two components are joined by an outgoing inventory node. Each component can be used as a standalone simulation tool to study intra-tier problems. When integrated, the three components form a complete supply chain simulation tool that can be used to support industry-level decision-making.

2.2.2 Sourcing and procurement model

The sourcing and procurement model simulates the interactions between a manufacturing facility and the suppliers of raw materials, reagents, and consumables. Various types of starting materials, ancillary materials, and consumables are used in an allogeneic cell therapy manufacturing facility, including cells, gene editing tools, beads, recombinant proteins, human plasma-derived media supplements, cryopreservation solutions, cryovials, bags, and other vessels, as well as other components that a manufacturer may have on its bill of materials. The company's inventory management plan may have different stock policies for each component. In the sourcing and procurement model, each material type will select from a set of commonly employed inventory control policies, including Periodic Reviewed Base Stock, Periodic Reviewed s-S, Continuous Reviewed Economic Order Quantity (EOQ), and Continuous Reviewed s-S. All policies are parameterized and allow the user to define the parameters. A list of selectable inventory control policies is summarized in Table 2.2**.**

Table 2.2 Selectable inventory control policies

Policy Name	**Example materials**	**Definable parameters**	**Example value**
Periodic Reviewed Base Stock Policy	Culture media	Base Stock Level	130 units
		Delivery lead time	7 days +/- std
		Recorder frequency	every 7 days
		Cost of delivery	10% of the material cost
		Cost of acceptance quality check	5% of the material cost
Periodic Reviewed s-S Policy	Culture media	Inventory-up-to level	130 units
		Reordering threshold	30 units
		Delivery lead time	7 days +/- std
		Recorder frequency	every 7 days
		Cost of delivery	10% of the material cost
		Cost of acceptance quality check	5% of the material cost
Continuous Reviewed EOQ Policy	Culture media	Reorder threshold	30 units
		Fixed reordering quantity	100 unit
		Delivery lead time	7 days +/- std
		Cost of delivery	10% of the material cost
		Cost of acceptance quality check	5% of the material cost
Continuous Reviewed s-S Policy	Culture media	Reorder threshold	30 units
		Inventory-up-to level	130 unit
		Delivery lead time	7 days +/- std
		Cost of delivery	10% of the material cost
		Cost of acceptance quality check	5% of the material cost

The sourcing and procurement model component forms part of the holistic supply chain model, but it can also be used independently to address problems that only involve supply chain-related issues. For example, the users may investigate cost efficiency and supply resilience under different stock policy combinations.

2.2.3 Manufacturing process

The manufacturing process model simulates the activities inside the manufacturing facility. The primary subgroups of activities in a cell manufacturing facility include manufacturing procedures, quality control procedures, and resource management. Figure 2.4 shows the flow chart of the generalized cell manufacturing process and how the resources are allocated to each step. The specimens from donors arrive at the top-left corner and go through the acceptance check and the upstream processing. Then the specimens enter a queue, waiting for bioreactors, operators, and reagents to be assigned by the resource management subsystem. After the necessary resources are allocated, the specimens come to the expansion stage, where several quality control tests are performed at different time points over the entire course. After the expansion, the products go through the downstream processing and release check subsequently. At last, qualified products are packed and sent to the warehouse for cryopreservation.

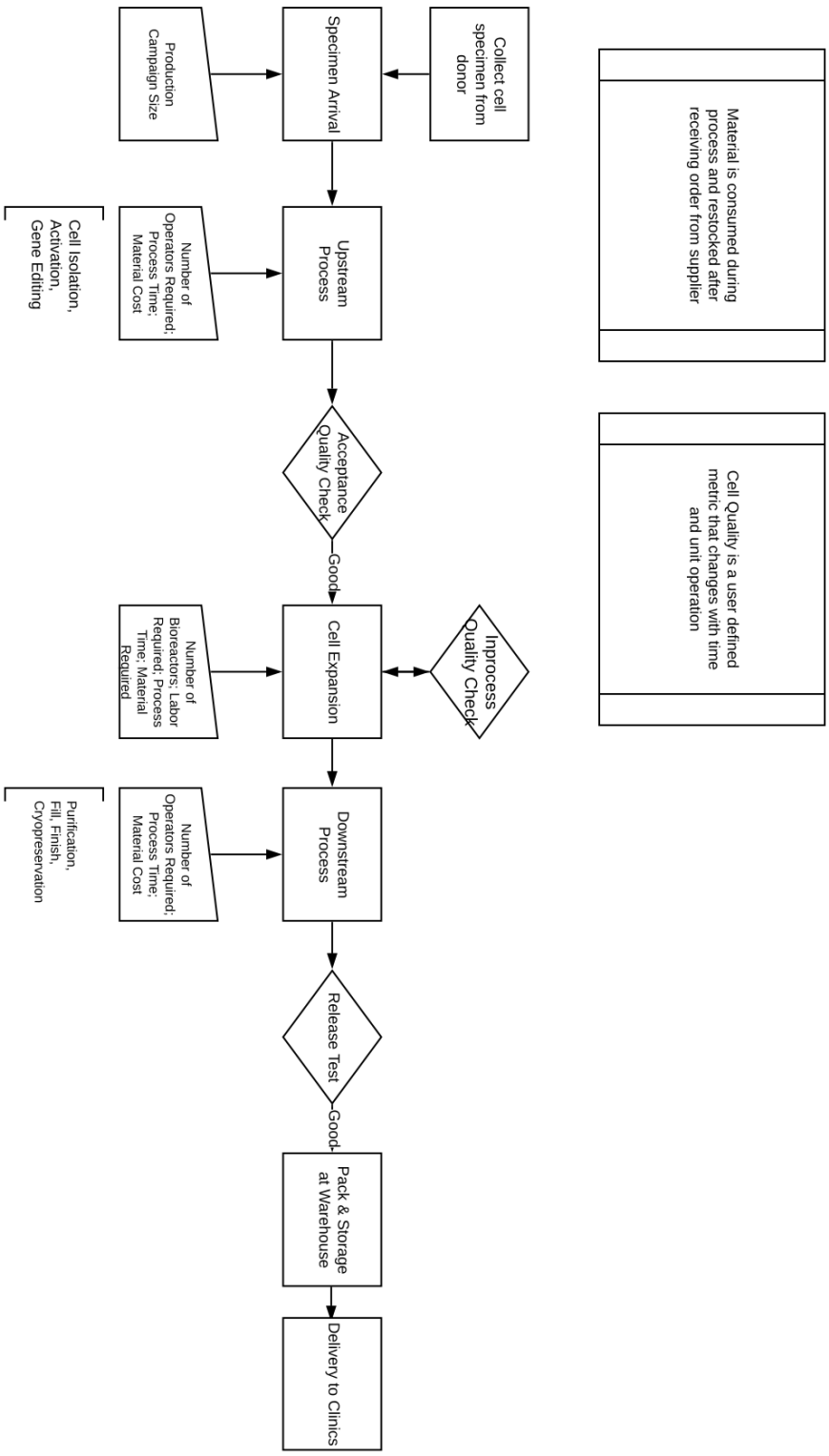

Figure 2.4 Process flow chart of allogeneic CAR-T cell therapies

There are a huge number of parameters needed to comprehensively define a cell manufacturing facility. However, in a typical decision-making scenario, only a subset of all the parameters would have significant relevance. The importance of each parameter depends on the specific problem of interest. In the generic simulation, a set of important parameters for common decision-making scenarios are selected. In the meantime, every agent is kept in the simulation expandable so that more detailed parameters can be called if they become important to the problem of interest. For example, if the total cost of human labor is concerned, only the "average salary" and the "total number of employees" will be used for calculation. However, if the problem is to compare the costs on technical staffs and management staffs, a set of more detailed parameters, including the number and salaries of different staff types, will be used.

The core parameters used in the generic simulation can be divided into six categories, according to QbD development strategies: Task, Employee, Equipment, Specimen, Operation, and Material. Table 2.3 summarizes the core parameters in each category.

Table 2.3 Core parameters used in the generic simulation

Name of parameter	**Category**	**Example value**
Campaign size	Task	8 batches per month
Dose per batch		100
Number of operators	Employee	6
Average tenure length		10 years
Shift length		8 hours
Number of working days per year		261
Cost of training		…
Average annual salary		$100,000
Number of non-operating staffs (QC, QA, supervising, admin, …)		20
Total number of bioreactors	Equipment	10
Probability of bioreactor breaking down		1% per day
Time needed for maintenance		5 days
Starting cell count	Specimen	2.25E9
Percent of CD4/CD8 enriched cells		27%
Gene editing efficiency		30%
Number of expansion fold per day		8
Cell loss at each unit ops		10%
Probability of contamination during unit ops		0.1%
Starting cell viability		uniform (80%)
Daily rate of cell losing viability		triangular (0%, 0%, -2%)
Operator required for upstream processing	Operation	3
Duration of upstream processing		2-4 days
Operator required for expansion		2
Duration of expansion		10-12 days
Setup time for expansion		3 hours
Active ops		4 hours every two days
Operator required for downstream processing		3
Duration of downstream processing		12 hours
Duration of acceptance test		3 hours
Viability threshold of acceptance test		87.675%
Duration of intermediate QC		1 day each
Viability threshold of intermediate QC 1		84.627%
Viability threshold of intermediate QC 2		83.224%
Viability threshold of intermediate QC 3		81.820%
Duration of release test		30 days
Viability threshold of release test		70%
Cost of QC		$30,000 per batch

Table 2.3 Continued

Cost of viral vectors per batch	Material	$ 9,000
Cost of culture media per batch per day		$400
Cost of activation		$700
Cost of reagent for purification		$300

2.2.4 Distribution and logistics

The distribution of allogeneic cell therapy is similar to the distribution of regular drugs. To simulate the distribution and calculate the time and costs, necessary information should include the number of warehouses and clinics in the supply chain network, the distance, delivery mode, time, and costs between each warehouse site and each clinic site. The requests generated from each clinic follow a Poisson distribution. Requests always go to the nearest warehouse with available therapies. There can also be hybrid solutions that use more than one basic design type in different regions or under different situations.

2.3 Demonstrative case studies for autologous cell therapy

A virtual CAR-T manufacture facility was built based on system specifications collected from an AuCT production facility with demonstrative case studies described in this section. A detailed case study for the design of an AlloCT production facility will be presented in **Chapter 4**.

2.3.1 Case 1: Optimal reagent base stock level

The aim of this case study was to determine an optimal base stock level for reagents in order to reduce the possibility of stock-out events while eliminating unnecessary inventory redundancy. In the simulation, the batch of all needed reagents was treated as a single unit of reagents. All other system specifications were fixed, while the base stock

level was varied from 10 to 150 in 10 step increments. Each base stock level is tested ten times with randomly generated starting seeds. To ensure appropriate comparison across different base stock levels, each of the ten times of simulations with different base stock levels is grouped as a master replication. Starting seed of each master replication must be kept identical to ensure that all event scenarios are the same except the variable of interest (base stock level). 110 data points collected from AuCT-Sim are scattered in Figure 2.5. The figure shows that average production lead time is monotonically decreasing as the base stock level increases, and the decreasing trend becomes mild when the base stock level exceeds 120.

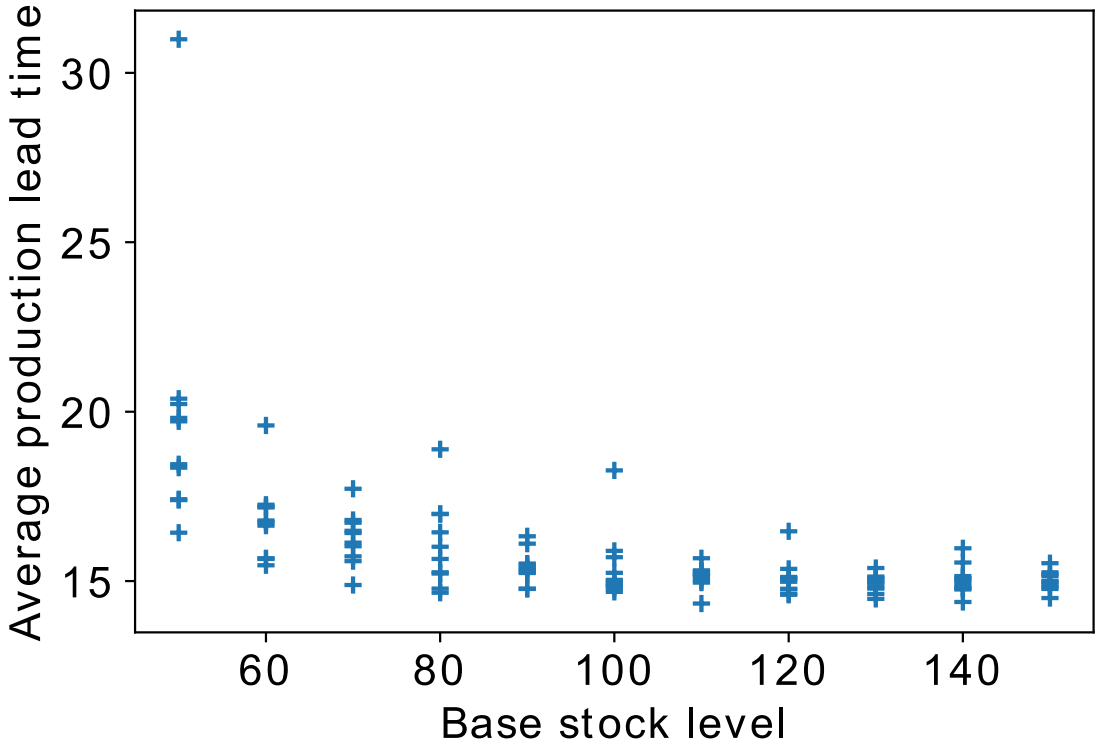

Figure 2.5 Base stock level vs. average production lead time

2.3.2 Case 2: Mitigating the risk and impact of supplier disruption

The target of this research case study was to investigate several system performances when a supplier disruption occurred and later recovered, with different combinations of the bioreactor and technical operator quantities. The system can then assist the designer in determining how many bioreactors and operators are needed to mitigate the risk of supplier disruption. Supplier disruption is a likely and severe risk for biomanufacturers. In 2017 alone, the cell therapy industry witnessed a saline shortage due to Hurricane Maria and a severe flu season (Jarvis, 2018; Wendelbo & Blackburn, 2018), as well as the shutdown of a major cell therapy supplier due to sterility issues (Palmer, 2017). The case study investigates how the system performance recovers after the occurrence of supplier disruption.

Figure 2.6 depicts queueing lengths of different facility designs over the horizon of 500 days. Queue lengths of every facility increased after the supplier disruption occurred on day 200, and queue lengths diminish after resuming the reagent supply on day 260. The facilities with 20 bioreactors, 12 operators, and the facilities with 15 bioreactors, 9 operators (black line and red dotted line, respectively) are able to recover to the normal state within 42 and 64 days, respectively. While for the facilities with 11 bioreactors, 7 operators, and the facilities with 11 bioreactors, 6 operators (purple line and blue dotted line, respectively), these fail to recover after the reagent disruption. Moreover, facilities with insufficient bioreactors or operators would also lead to further mild increments in their queue lengths. This fact is because of the congestion of pending requests, as the constrained number of bioreactors are not able to clear the cumulated requests during the disruption periods.

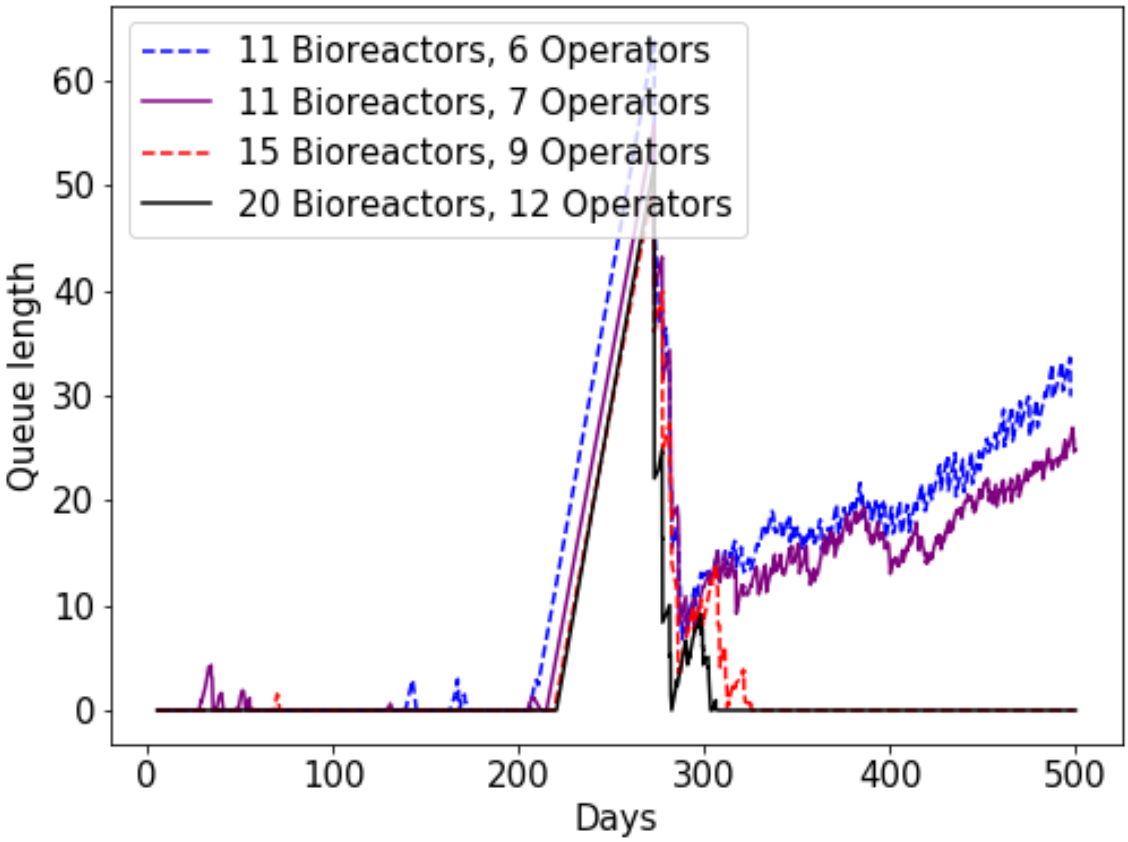

Figure 2.6 Trends of queue lengths for different facility designs

Figure 2.7 summarizes a few of the KPIs used to evaluate system performances for cases with 11 bioreactors and 7 operators (6a) and 20 bioreactors and 12 operators (6b). As shown in Figure 2.7a, when 11 bioreactors and 7 operators are equipped, the supply chain fails to recover after the supplier disruption from Day 200; the bioreactor utilization is kept at 100%, and the proportion of patients who canceled their production increases eventually to nearly 20%. The proportion of patients queued also increases to 37% by the end of Day 500.

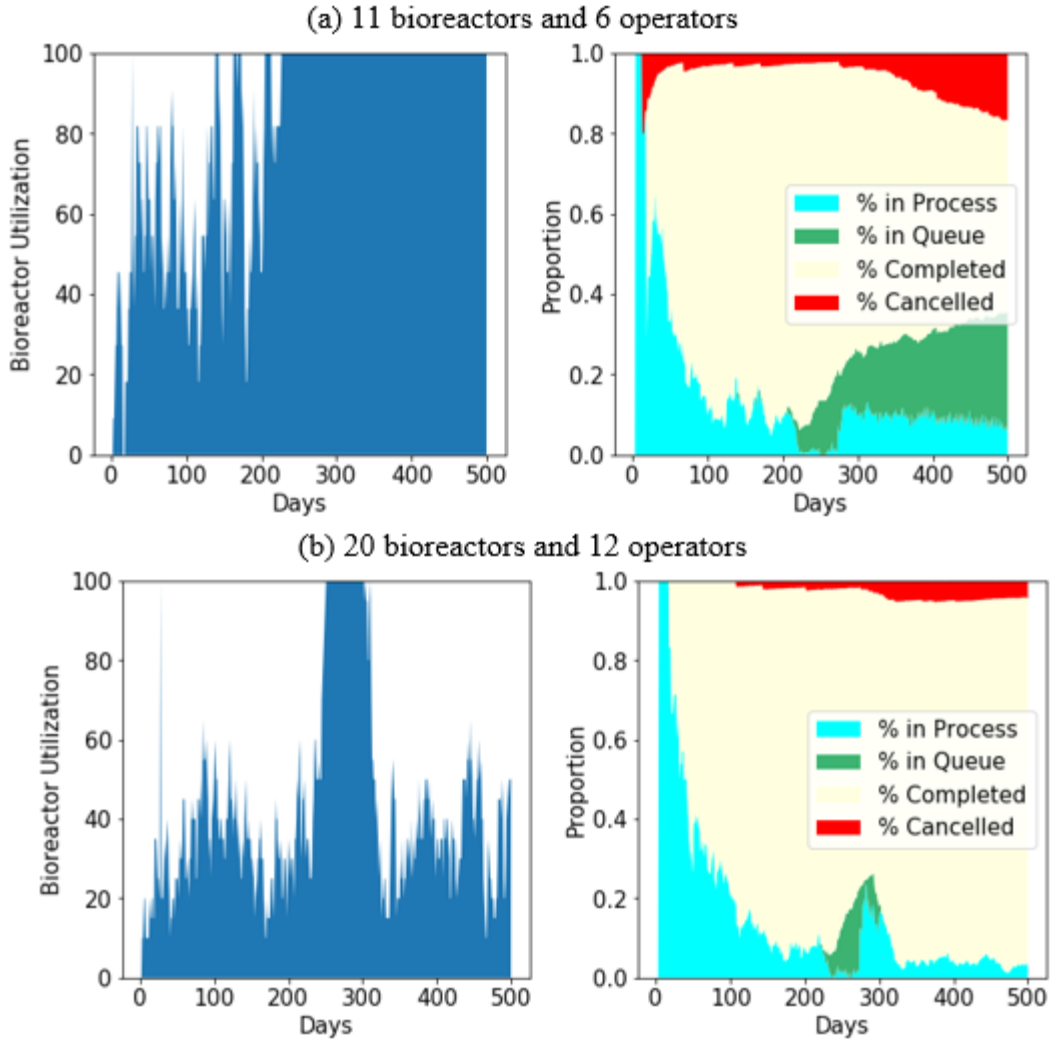

Figure 2.7 System performance under selected equipment and labor force specification

While for the system equipped with sufficient bioreactors and operators (20 bioreactors and 12 operators in Figure 2.7b), the bioreactor utilization rate recovers to normal on Day 334. The proportion of patients who canceled their production barely increased by about 3 percent and then mildly recovers to normal by the end of the testing period. The proportion of patients queued increases to 29% after the disruption occurred, but is able to recover quickly to normal by day 320.

By carefully tuning bioreactor and operator quantities, the decision-maker can visualize the recovery ability under given system specifications and design strategies to mitigate the risk of process disruption.

2.4 Discussion

As an emerging industry, cell therapy manufacturers must engage in data-driven planning before expansion. However, high uncertainty, the steep upfront investment, and the lengthy trial duration make practical verification of planning scenarios impractical. Running computational experiments with a simulation model becomes an economical alternative for several reasons.

Firstly, the simulation platform generates and records data comprehensively with perfect repeatability. In real-life experiments, some critical data could be overlooked at the beginning due to the lack of fundamental knowledge. With computational experiments, all data are stored and can be regenerated. Although some parameters are stochastic, recording the seed of the random number generator ensures that repeats generate the same "random" values.

Secondly, factors in the platform are controllable. In real-world manufacturing demonstrations, it is challenging, if not impossible, to isolate one particular factor from numerous factors in a cell therapy manufacturing facility to test its effect. The effect can be confounded with the considerable variability in other factors. With simulation, it is easy to vary one factor in multiple computational experiments to evaluate its actual effect.

Thirdly, the simulation platform can be used to investigate hypothetical scenarios. The simulation can provide insights into events that are too large in scale to set up a real-life experiment, such as a hurricane-caused reagent supply disruption that affects the entire

east coast of the US. Decision-makers can use this decision support system (DSS) to test different risk mitigation strategies and be prepared to counter similar events in the future.

Lastly, the simulation platform can highlight and clarify ethical tradeoffs inherent in the complex CAR-T cell manufacturing processes. The focus of supply chain optimization is typically and understandably meeting anticipated demand while minimizing the cost of goods. Decisions about the number of manufacturing facilities to use, their locations, and their capacity, among many other factors, also affect the extent to which patients or subsets of patients can access a specific therapy safely, reliably, and promptly. Such information is critical to firms developing strategies to scale their production and incorporating potential contingencies into their planning processes. Supply chain simulation, combined with information on the possible size, location, and prognosis of patient populations, in particular, may offer a uniquely powerful approach to proactively identify concerns relevant to the commercialization of novel cell therapies early in the development process and proactively address them.

Because the framework is highly customizable, it is a versatile tool that can help with the study of various subjects. Future research directions following this work include:

- What is the optimal patient priority policy for compassionate care cases?
- What is the best transshipment strategy for the robustness of the supply chain network?
- Which inventory replenishing policy is the most suitable for a cell therapy facility, considering the possibility of supply disruptions?
- How to make policies to encourage manufacturers to expand into regions with low patient accessibility?

- What are the marginal effects of technical innovations in different manufacturing and quality control procedures?

CHAPTER 3 COST ANALYSIS FRAMEWORK FOR CELL THERAPY

3.1 Background

Although more and more cell therapies are getting approved by FDA and other regulatory agencies around the world, the treatment itself remains prohibitively expensive for most of the targeted patients. As of March 2021, there are five FDA-approved CAR-T therapies for treating different types of blood cancer, including leukemia, lymphoma, and most recently, myeloma (U.S. Food and Drug Administration, 2021) for both children and adults. The cost of these therapies ranges from $373,000 to $475,000 (Table 3.1).

Table 3.1 FDA approved CAR-T therapies for blood cancers as of April 2021

Product	**Company**	**Year Approved**	**Price**
Kymriah	Novartis	2017	$475,000 $373,000
Yescarta	Gilead/Kite	2017	$373,000
Tecartus	Gilead/Kite	2020	$373,000
Breyanzi	BMS	2021	$410,300
Abecma	BMS & Bluebird Bio	2021	$419,500

However, the price of the drug itself is just a part of the total treatment cost. A typical CAR-T treatment for blood cancer includes pre-treatment testing, apheresis, conditioning, treatment, post-treatment monitoring, and post-discharge monitoring. These processes result in a lengthy hospital stay and the use of many other services and medicines. The combined cost of the drug and these related care is estimated to be somewhere between

$463,500 - $968,000, close to one million dollars for some patients (Rockoff, 2018). The unprecedented high cost of the treatment has created great financial strains for hospitals, health insurers, and patients themselves as they figure out how to cover the astronomical cost. Many health insurers are only approving CAR-T therapies on a case-by-case basis, and a lot of the patients have turned to online medical crowdfunding, such as the use of the GoFundMe website, to secure funding for the medical expenses incurred during the treatment (Ho, Oso, & Levine, 2019). Therefore, understanding the manufacturing cost and its relationship to price is the first step to make the treatment more affordable.

This chapter will establish a cost analysis framework for understanding the cost of cell therapy, compare and analyze different cost analysis models, set the benchmark for manufacturing costs, and integrate cost modules into the existing simulation platform.

3.2 Understanding cell therapy cost

3.2.1 Cell therapy cost overview

Based on the development cycle of a pharmaceutical product, the overall cost and investment for developing and producing a cell therapy product can be broken down into three major categories: development cost, manufacturing cost, and operation cost (Farid, Baron, Stamatis, Nie, & Coffman, 2020). A breakdown of what these costs entail is listed in Table 3.2.

Table 3.2 Major cost categories in the development cycle of a pharmaceutical product

Development Cost	**Manufacturing Cost**	**Operation Cost**
R & D Cost	Direct Cost	Logistic & Distribution Cost
Clinical Trial Cost	Indirect Cost	Sales and Marketing Cost
Factory Capital Cost	Other Cost (Failure Cost)	Administrative Cost
Regulatory Compliance Cost		Patient Administration Cost

Development costs are the costs incurred to the manufacturer before the product hits the market. These costs include the expenditure for research and development (R & D) of the therapy, capital costs incurred for building the manufacturing facilities and setting up the logistic network, costs for designing and running clinical trials, including manufacturing of the therapy for the clinical trial, as well as the costs associated with ensuring the drug design, manufacturing, and clinical trial processes are compliant with the regulation of FDA and other regulatory bodies.

Manufacturing costs can be divided into direct costs that are directly tied to the specific batch manufacturing process, indirect costs that are not tied to the specific manufacturing process, and the costs incurred for the failed batches that cannot be sold to the patients.

Operation costs are the costs incurred outside the manufacturing facilities when the product is released to the market. These costs include the logistic and distribution costs for getting the cells to the clinic, sales and marketing cost for raising awareness and promoting the drugs to the targeted patients, administrative costs, as well as patient administration cost for training and assisting hospitals on how the drug should be administered.

There is no standard for how the costs need to be categorized, and different cell therapy companies can have different cost categories among each other. Some cell therapy companies categorize logistic costs as parts of manufacturing costs instead of operation costs.

3.2.2 Manufacturing cost breakdown

As the purpose of this research is to help cell therapy manufacturers improve their production and logistic operation, the thesis will focus on the modeling of cell therapy manufacturing costs within the manufacturing facility. Manufacturing costs for cell therapy production mainly come from the following major sources: personnel, raw material and supplies, quality, facility & maintenance cost. Each of these cast categories has some components that contribute to the direct costs, indirect costs, or failed costs. Some of the cost components for each of these cost categories are listed in Table 3.3.

Table 3.3 Detailed breakdown of manufacturing costs

	Direct Cost	**Indirect Cost**
Personnel	Operator and quality control labor wage and benefit	Operator and quality control training, pension, overhead, supervision and management wage and benefit
Utilities	Electricity, water, natural gases use during activity	Electricity, water, natural gases use at rest
Facility & Maintenance	Corrective maintenance	Preventive maintenance, rent, investment amortization (non-cash cost)
Quality	Quality testing, validation, and documentation	Cleaning, disinfection, environment monitoring, planning, qualification
Materials and Supplies	Raw material and reagent, cleanroom garments	Office and lab supplies, cleanroom garments
Cost of Failed Batch (failed quality testing, contamination, or past shelf life)		

The price for some of the cost items, such as cleanroom garments and utility costs, are fairly transparent and consistent. They are easy to look up in the marketplace, and the price does not vary much across different regions, while some other costs are more elusive and can vary a lot between factories. For example, the cost for training cell therapy operators is dependent on the skill set of the new hire and how much resources the manufacturer is willing to dedicate for training, making it hard to estimate and are determined case-by-case. All cost components are categorized into three groups based on their transparency and variation among different companies (Figure 3.1):

- Category 1 Cost, where the cost is transparent and fairly consistent across the industry. This might include equipment and starting materials.

- Category 2 Cost, where the cost lacks industry data or has a large range between companies. This might include gene-editing tools, QC testing, some ancillary materials.
- Category 3 Cost, where the cost is either proprietary or depends on company policies. This might include the upstream/downstream process itself.

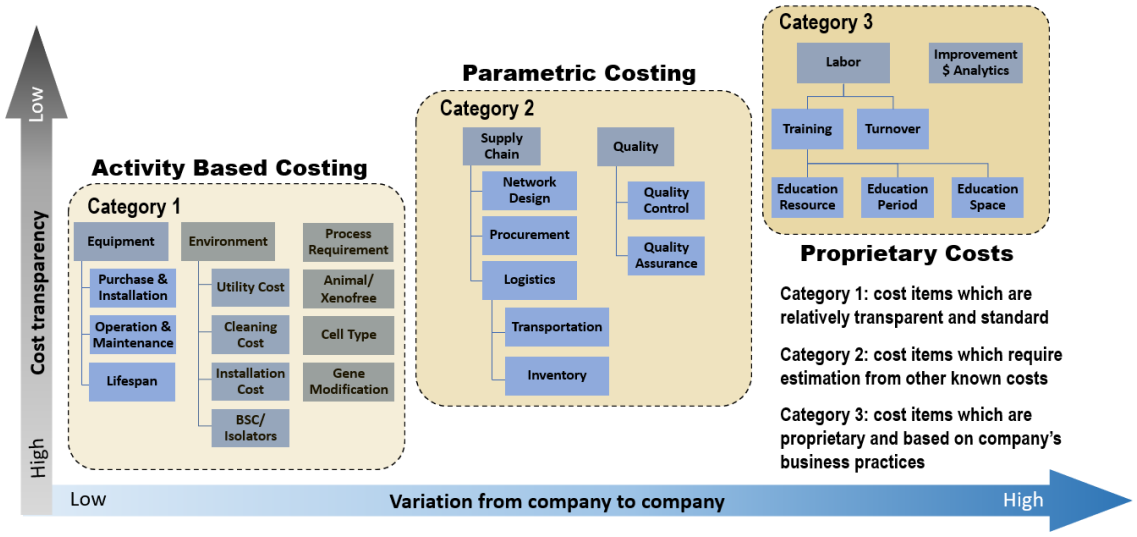

Figure 3.1 Categorizing cost items based on the opaqueness and degree of variation

3.2.3 Cost estimation methodology

Cost items with different transparency require different methods to obtain or estimate the process information. These methods can include:

- Publicly available information (news, press release, financial disclosure)
- Online marketplace
- Market report & analysis from market research companies
- Industry survey report

- Direct correspondence with manufacturers
- Commercial database
- Simulation software
- Heuristics and estimation factors
- Similar products or historical data
- Best guess

The list is ordered based on the transparency and the accuracy of the cost items. Researchers doing cost estimation should start with searching for publicly available information and gradually move down the list.

For example, the facility construction costs of a CAR-T manufacturing facility with an annual production capacity of 5,000 batches can be found from publicly available information on Kite's SEC filings (Kite Pharma, 2016) to be around $26 million for their El Segundo manufacturing facility. Many equipment costs can be found by searching online marketplace such as Alibaba.com or requesting a quote from equipment manufacturers. Researchers can also try reaching out to the cell therapy manufacturer directly to ask for an estimation of certain cost items or look up industry survey reports based on the response from actual cell therapy manufacturers to estimate many of the cost items (Lipsitz et al., 2017). If there is an additional budget for cost modeling, researchers can purchase commercial market reports from market research companies that contains a lot of cost information. There are also commercial databases and process simulation software, such as Biosolve Process® that contain many cost item information.

For cost item information that cannot be directly obtained, researchers can use heuristic and estimation factors to estimate the cost. Lang factor is a very popular

estimation method widely used in industrial engineering to calculate the capital and operating costs of a manufacturing plant based on total equipment cost. Many cost analysis research articles have used a Lang factor of 23.67 to estimate the facility costs for CAR-T manufacturing facility (Hassan et al., 2015; M. Jenkins, Bilsland, Allsopp, Ho, & Farid, 2016; Pereira Chilima, Moncaubeig, & Farid, 2018; Simaria et al., 2013). If none of these methods are available, researchers can resort to finding the cost items for similar products or historical data for estimating costs, such as using the quality control cost of mesenchymal stem cells to estimate the quality control cost of CAR-T cells.

3.2.4 Variations in cost estimation

Many academic research articles have been the cost of goods (COGS) estimation of different cell therapy products. A list of the cost of goods estimation studies from peer-reviewed journals is in Table 3.4 that includes CAR-T, MSC, iPSC, dendritic cells, and other lymphocytes that originate from either an autologous or allogeneic donor source. COGS are defined as the manufacturing cost for one dose of cell therapy. The COGS of a cell therapy product vary widely, ranging anywhere from $1,000 to $120,000. For autologous cell therapy, one batch can only produce one dose for the intended patient, while a batch of allogeneic cell therapy can be divided into several doses. Thus, the COGS of allogeneic cell therapy are usually lower than autologous cell therapy and are heavily dependent on dose requirements. For example, treatment for chronic low back pain requires around 10 million cells per dose (Pang, Yang, & Peng, n.d.), while treatment for systemic diseases such as GvHD or heart disease can require up to 1 billion cells per dose (Lazarus et al., 2005; Lin & Hogan, 2011), resulting in over 100 fold difference in COGS for treatment.

Table 3.4 List of COGS estimation for cell therapy products from peer reviewed literatures. Costs that are originally in other currencies are converted to USD

Product	**COGS**	**Reference**
Autologous CAR-T	$78,720	(Lopes, Noel, & Sinclair, 2020)
Autologous CAR-T	$58,200	(Spink & Steinsapir, 2018)
Autologous CAR-T	$95,780	(Harrison et al., 2019)
Allogeneic CAR-T	$4,460	
Allogeneic CAR-T	$7,629	(M. J. Jenkins & Farid, 2018)
Allogeneic umbilical cord derived MSC	$3,700 - $65,100	(Mizukami et al., 2018)
Allogeneic MSC	$485 - $1,750 (10M cells) $13,134 - $111,488 (1 B cells)	(Pereira Chilima et al., 2018)
Allogeneic MSC	$1,000 - $2,000	(Harrison, Medcalf, & Rafiq, 2018)
Autologous dendritic cells	$51,301	(Lopes et al., 2018)
LV induced autologous hematopoietic stem cells	$54,148	(Abou-El-Enein et al., 2013)
Allogeneic tolerogenic dendritic cells	$41,221	(ten Ham et al., 2020)
Allogeneic pp65-specific T cells	$27,371	
Allogeneic MSC	$36,461	
Allogeneic stem cell-derived NK cells	$57,943	
Autologous monocyte-derived macrophages	$40,398	
Allogeneic limbal stem cells	$28,463	
Allogeneic cytotoxic T cells	$10,306	

Even for the same cell type, the COGS estimation can have big variations. The three COGS estimations for autologous CAR-T cited in Table 3.4 range from $58,200 to $95,780. Some of the variations result from different factory sizes and designs, different manufacturing routes, equipment choices, and personnel management, while some of other

variations result from different valuations for the same cost items. Table 3.5 lists the major differences in the three COGS estimation methods for autologous CAR-T cells published in peer-reviewed journals. Some of the cost item values are approximated from the figures in these publications and may not match exactly with the publication.

Table 3.5 Comparison of COGS estimation studies for autologous CAR-T cells

	(Harrison et al., 2019)	(Spink & Steinsapir, 2018)	(Lopes et al., 2020)
Market			
Annual demand	17,955 (USA)	1,500	5,000
Market estimation method	Assumed CAR-T captured 30% blood cancer market, and the provider captured 35% of the CAR-T market	Kite Pharma press release of Yescarta plant	Similar products
Cost items source	Direct correspondence	Database & simulation software	Similar products
Total manufacturing cost			
Total annual cost	$1.72 B	$87.3 M	$800 M
Total cost per dose/COGS	$95,780	$58,200	$78,720
Largest cost category	Material and supply (65% COGS)	Labor (71% COGS)	Material and supply (67% COGS)
DETAILED COST CATEGORY			
Labor			
Average annual cost per employee	$90,000	$155,000	$97,333
Number of staff	160	400	1654
Total labor cost	$14.4 M	$62 M	$161 M
Labor cost per dose	$803	$41,322	$15,691
Percent of COGS	1%	71%	19%
Cost items included	Operator wage, pension, overhead, training, turnover	clinician, courier, operator, supervisor, QC, QA compensation	operator, QA, QC, supply chain, and facility manager compensation
Material and supply			
Total cost	$1.1 B (mfg) $0.55 B (QC)	$15.7 M	$530 M
Per dose cost	$62,257 (mfg) $30,647 (QC)	$10,476	$51,744
Percent of COGS	65% (mfg) QC (32%)	18%	67%
Facility and transport			
Total cost	$17.2 M (facility) $34.6 M (transport)	$10.5 M (facility)	$108.1 M (facility) $7.7 M (transport)
Per dose cost	$960 (facility)	$6,984 (facility)	$10,540 (facility)

Table 3.5 Continued

	$1,920 (transport)		$750 (transport)
Percent of COGS	1% (facility) 2% (transport)	12% facility	29% (facility) 2% (transport)
Total installed capital	N/A	$37 M	$277 M
Cost items included	site, equipment, utilities, waste, logistic cost	capital amortization, maintenance, utilities, transport not included	capital amortization and logistics, insurance, maintenance, utilities

The variations in COGS estimation comes from having different estimation for market demand and production capacity, having different sources for cost item valuation and different cost items included in each category. Spink & Steinsapir has labor as the largest cost category accounting for 71% of the total COGS, while the other two models pegged labor for only 1% and 19% of COGS mainly due to different definitions of labor. Only Spink & Steinsapir included clinicians, couriers in the model, while Harrison et al. only included operators in the cost model and has QA, QC personnel separated in its own category. Spink & Steinsapir also has a much lower material cost compared to the other two models as they assumed a very low viral vector cost that only accounts for 3-4% of material cost, while the other two models assumed a much higher viral vector cost that account for more than 20% of material costs.

Using cost item data from all the published literature featured in Table 3.4, as well as data collected directly from cell therapy manufacturers and other sources, a set of possible ranges for the total cost of each cost category in autologous CAR-T manufacturing was determined and shown in Figure 3.2. In the figure, the top and bottom boundaries of the bar graph represent the maximum and minimum cost for that cost category, with the

blue line denoting the estimated industry average cost using the simulation platform that will be described in detail in the next section.

Figure 3.2 Variation in cost per dose for each cost category for autologous CAR-T

The material cost has the largest variation among all cost categories, followed by labor and then facility cost, while transport has the smallest variation. Cell therapy manufacturers can compare their cost with the range and determine if their cost is at a higher or lower position compared to the rest of the industry.

As the material cost has the largest variation, it has the largest potential for cost reduction. The material cost is highly dependent on the size of the supply base and the scale of the supplier. Finding a large supplier with a lot of competitors can greatly reduce the material cost and overall manufacturing cost.

Manufacturers with a large labor cost should focus on improving labor utilization rate, cross-train and share operators with other production lines, and look for possible ways to outsource many production functions, such as outsource viral vector production, some QC tests, and distribution to third parties.

3.3 Cost modeling

All the cost modeling described in the previous section is developed on a framework and does not adequately capture the stochasticity and complexity of the manufacturing process. To account for the variation in cost estimation and help cell therapy manufacturers better estimate the cost of their production facility, this research will integrate a cost modeling module into the simulation platform and establish a benchmark for the cell therapy manufacturing cost that can help manufacturers ensure a cost-effective design of the production facility.

To establish a benchmark for each cost item, detailed cost information was collected from published literature, academic and industrial cell therapy manufacturers, and suppliers and stored in a database containing over 300 cost items for different cell therapies. Based on the variation and reliability of the cost items, the costs are categorized as Category 1, Category 2, and Category 3 cost described in the previous section. A different cost estimation model is employed for these different categories.

For the Category 1 cost components, the *activity-based definitive cost model* is used to determine cost. As the manufacturing and distribution of cell therapies can be affected by the patient status in real-time, the cost of an ongoing product will increase only when the particular resource is transformed into the added value of this product. For example, the cost of reagents, consumables, and labor hours of the upstream process is only added

to the overall manufacturing cost once the upstream process has been completed in the simulation model (Figure 3.3). If there is a discrepancy in the value of the cost items, either the average value of the cost is used, or a reasonable value is picked based on outside experts' opinions.

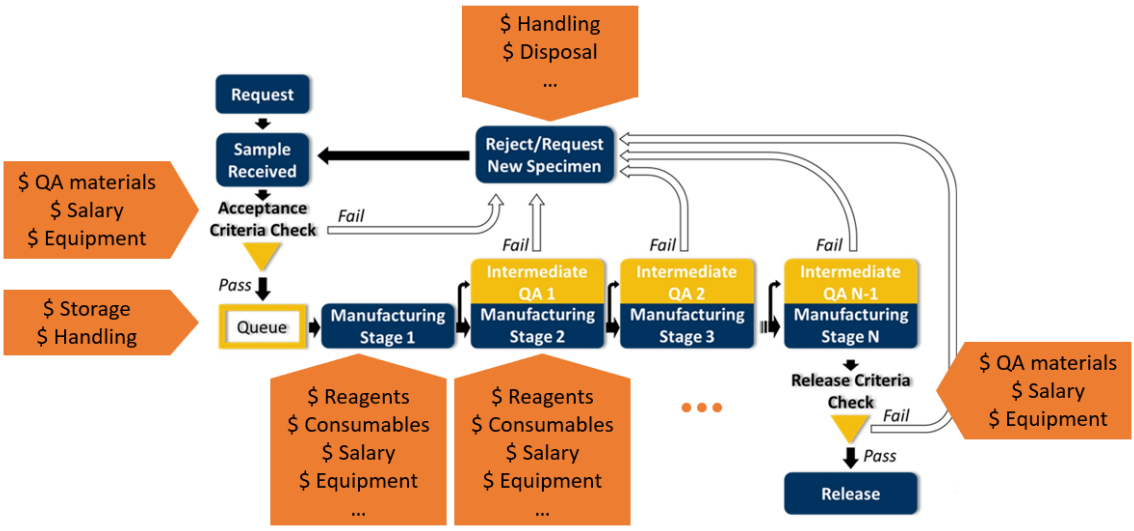

Figure 3.3 Definitive activity-based cost model for cell therapy

For the Category 2 cost components, the *parametric-based cost model* is used to estimate cost. A set of parameters that affect the cost component are first defined and assigned a range based on the information collected. The users will input the parameters, and the model will use heuristics to calculate the range of the cost component. For example, when the details of the logistics are not clear, users can estimate the logistic cost by setting the logistic cost to be 2% of manufacturing cost based on survey data.

The Category 3 cost components will be fully user-defined with reference and suggested value based on similar products or historical data.

Based on these criteria, a cost modeling module is developed for the simulation platform. The simulation platform takes in a database file containing all the cost items involved in the particular cell therapy manufacturing process following the flowchart described in Figure 3.4. For example, a Category 1 cost item such as the viral vector used in the autologous CAR-T manufacturing process is coded in the following logic, the unit price of the viral vector is $8,492; one unit of the viral vector is used per batch; the viral vector is a part of the material cost; the price is definitive, and it is a direct cost in the manufacturing process; it is added during the upstream processing. The logic for a parametric cost item such as operator training cost is as follows: each operator receives one training session; it is part of labor cost; it is parametric; it is indirect; it happens once a year; it is 2% of annual salary, and the annual salary is $100,000. The training cost will be added to the total cost in the simulation once a year.

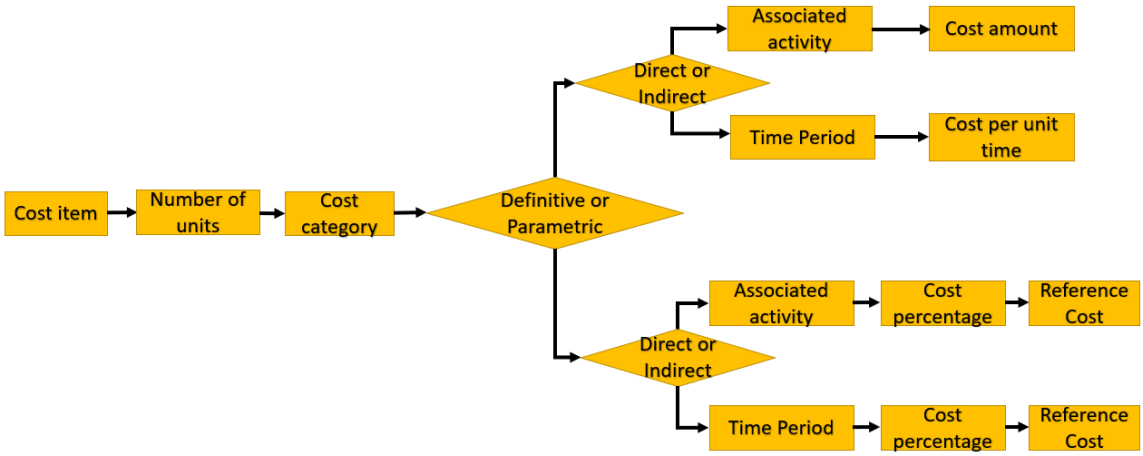

Figure 3.4 Flowchart of inputting cost data into the simulation platform

Following the logic described above, each cost item for autologous CAR-T is added to the simulation, and the simulation is run 1,000 times to produce a cost estimation for autologous CAR-T. Based on the simulation experiment results, the COGS for an autologous CAR-T product from a factory that produces 18,000 batches per year is estimated to be $83,309 ± $2,839 with an annual operating cost of $1.5 billion. Material accounts for the largest cost of 62%, followed by 19% labor cost, facility, and failure costs, with transport cost accounting for 1% (Figure 3.5). The result is consistent with other publications and fits well within the range of cost estimation described in Figure 3.2.

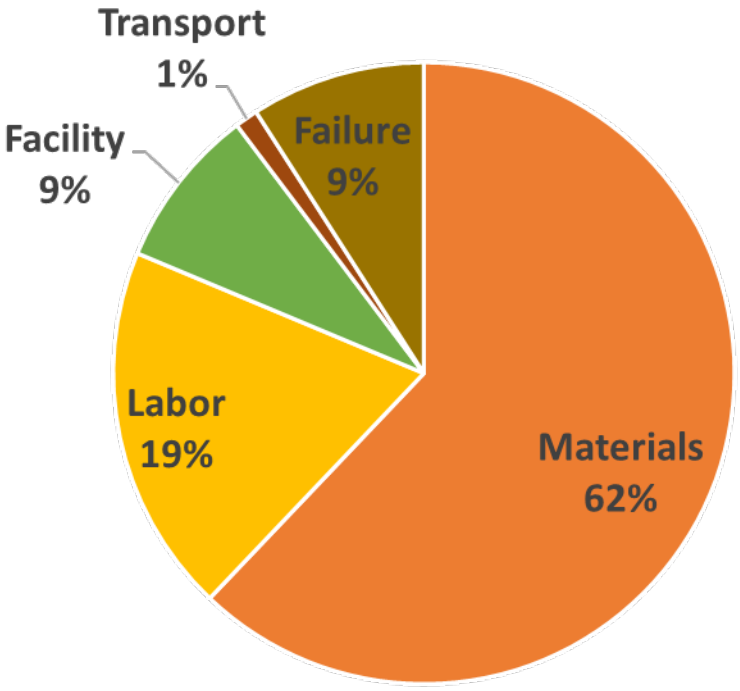

Figure 3.5 Estimated cost breakdown of autologous CAR-T

The cost for other cell types, including allogeneic MSC cells and iPSC-induced retina pigment epithelial cells, was also estimated using the same methodology. The cost estimation for the allogeneic MSC cells will be described in detail in **Chapter 4**. The summarized cost estimations for each three cell types are described in Table 3.6.

Table 3.6 COGS estimation for different cell types

Product	CD19 CAR T-Cells	MSC based cartilage graft	iPSC induced retinal pigment epithelium cell
Indications	Leukemia & lymphoma	Joint cartilage defect	Age-related macular degeneration
Product Origin	Autologous peripheral blood	Allogeneic bone marrow	Allogeneic peripheral blood
Manufacturing Time	14 days	52 days	117 days
Batches per year	1,800	400	100
Doses per batch	1	250	100
Cost per Batch	$83,309	$70,901	$29,834
Cost per Dose	$83,309	$276	$298

3.4 Demonstrative case studies

Demonstrative case studies are presented in this section to showcase how the cost module can be used to improve manufacturing cost

3.4.1 Case 1: Cost impact of resource underutilization

This study aims to understand how much additional costs are incurred when the manufacturing facility is underutilized and whether the manufacturer should focus on improving labor or equipment utilization.

In this simulation, an autologous CAR-T manufacturing facility with an annual production capacity of 1,500 batches is modeled to have an estimated COGS of $85,867. The facility requires a minimum of 34 full-time operators and 45 bioreactors to meet the production capacity based on simulation results.

However, the market demand is weaker than expected, and only around 1,000 orders are placed in a year. If the facility keeps the same number of operators and bioreactors, the estimated COGS is estimated to increase to $87,566, increasing COGS by $1,763. If the facility can remove bioreactors to maximize utilization, it will save $196 per batch. However, if the facility can divert some of the labor to other production lines and maximize labor utilization, it will save $1,128 per batch on COGS. In this situation, the facility should focus on increasing labor utilization by diverting operators to other production lines (Figure 3.6).

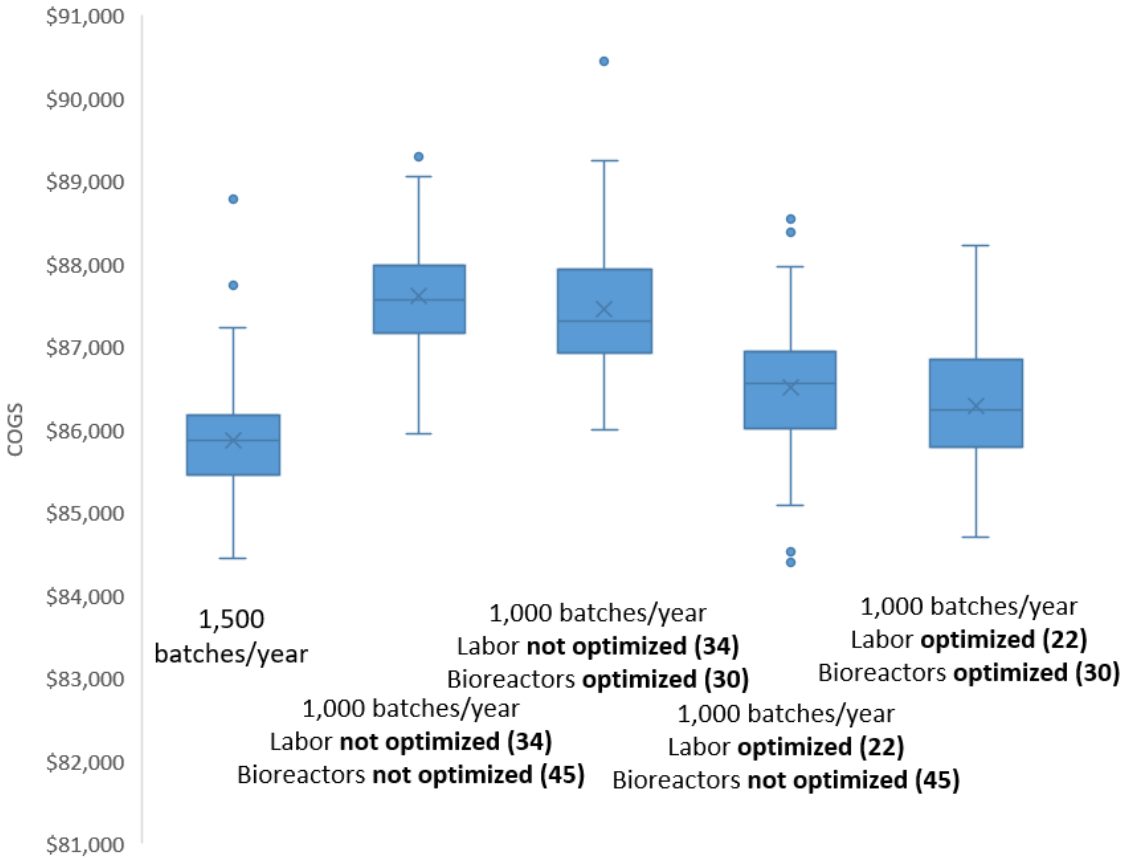

Figure 3.6 Impact of labor and equipment underutilization on COGS

3.4.2 Case 2: Evaluating cost impact on new gene transfer technologies

The aim of this case study is to evaluate the viability and competitiveness of new gene transfer technologies for manufacturing cost reduction.

One of the most expensive cost items in CAR-T manufacturing is the cost of viral vectors. Current CAR-T manufacturers mostly use either lentiviral vectors or retroviral vectors to transfer the CAR gene to the T-cells. However, manufacturing of these viral vectors is extremely complicated, and they also require extensive safety tests to ensure they can be used safely for therapy purposes (Ausubel et al., 2012; Levine et al., 2017). There is a great demand for new gene transfer technologies that are easier and cheaper to

manufacture than viral vectors. One of the most promising new gene transfer technologies currently in development is the transposon/transposase plasmid DNA transfection (Ramamoorth & Narvekar, 2015). The manufacturing process is simpler and cheaper than the viral vector, and the transposon does not require extensive biosafety testing. However, a current drawback in the transposon system is that it requires a much longer cell expansion time than the current manufacturing process (Singh et al., 2011), increasing resources required for expansion.

In this case study, a simulated CAR-T manufacturing process is built for each gene transfer technology with lentiviral vectors, retroviral vectors, and transposon system with the detailed input parameter included in Table 3.7.

Table 3.7 Input parameters used for the three gene transfer system in the simulation

	Lentiviral Vector	**Retroviral Vector**	**Transposon System**
Average gene transfer efficiency (%)	40.4% ± 20.5%	59.8% ± 21.4%	85.5% ± 8.1%
Lead Time (days)	14	14	28
Cost	$8,492	$7,635	$1,400
Failure Rate at 10% efficiency threshold (%)	7%	1.1%	0%

The average gene transfer efficiency for each method is calculated from 297 published clinical trial data that use these systems for manufacturing CAR-T (Hartmann, Schüßler-Lenz, Bondanza, & Buchholz, 2017). The costs of the viral vector and transposon

system are based on the data from published literature (Abou-El-Enein et al., 2013; Hudecek & Ivics, 2018; Spink & Steinsapir, 2018). If the gene transfer efficiency falls below 10%, the product will fail the QC process and be rejected.

After running the simulation, the result shows that although the transposon system can greatly reduce the gene transfer cost, it is not enough to offset the increase in expansion cost due to the longer expansion requirements (Figure 3.7). Using a transposon system currently will cause an increase of around $6,900 in COGS.

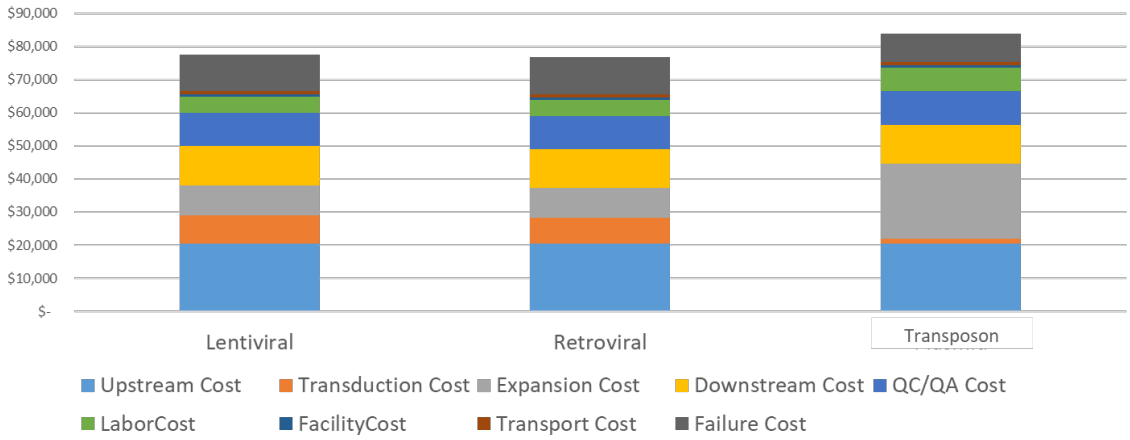

Figure 3.7 COGS breakdown of CAR-T manufacturing using different gene transfer methods

Although the transposon system used in this study does not provide a cost advantage to CAR-T manufacturing, there have been many promising research efforts to enhance the transposon system that can reduce expansion time (Hudecek & Ivics, 2018; Monjezi et al., 2017). Using the simulation platform, it is calculated that the transposon system will be more cost-effective than the viral vector if the expansion duration can be reduced to 14 days from the current 18 days in the study (Figure 3.8).

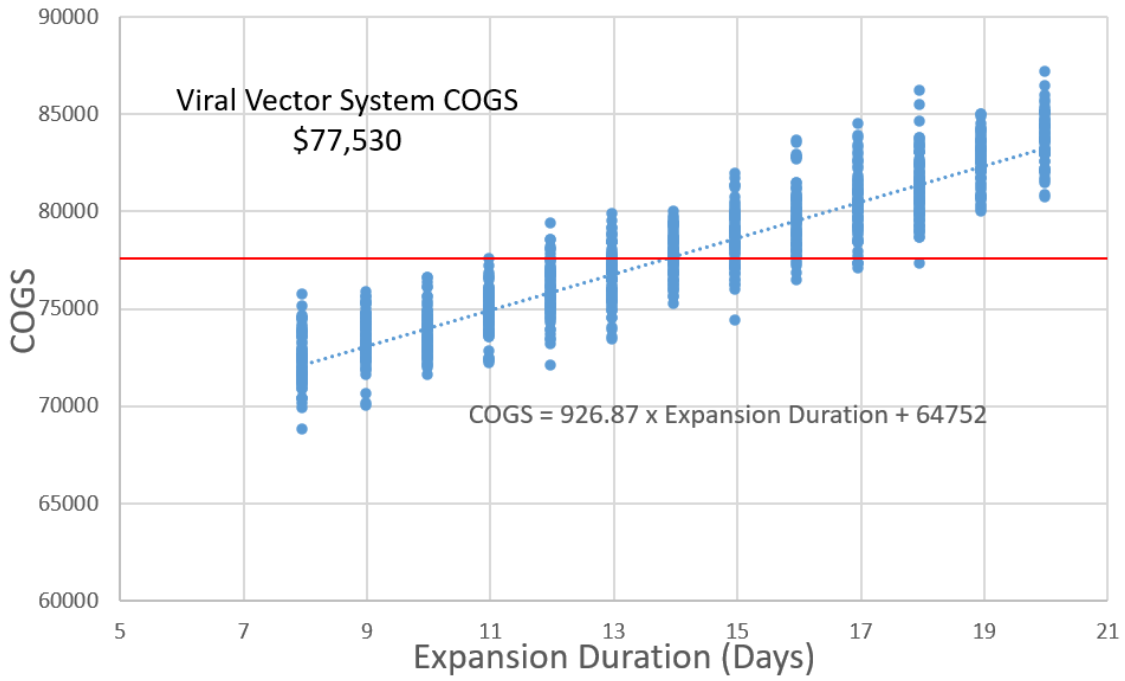

Figure 3.8 Impact of expansion duration on the transposon system COGS

3.4.3 Case 3: Centralized vs. decentralized manufacturing

The aim of this study is to develop a rudimentary network model to compare operation costs for building a centralized or decentralized manufacturing network in the US. The case study will use the Kymriah CAR-T product from Novartis as the basis to model the demand and logistic network for the simulation.

In this study, three different manufacturing networks are planned to meet an annual demand of treating 2,000 patients within the contiguous United States. The three networks include: 1) Building one centralized facility with a production capacity of 2,000; 2) Building two regional manufacturing hubs around the East and West Coast; 3) Building ten decentralized facilities around the country.

Thirty clinics that offer CAR-T treatments are selected at random from the CAR-T clinic locator on the Novartis website (Novartis AG, n.d.). The clinic list is included in

Appendix Table A.01. The annual demand of each clinic is calculated based on the total population of the state and the number of CAR-T treatment centers in that state. If there is no CAR-T center within a state, then the patients from that state are assumed to go to the closest out-of-state CAR-T facility for treatment. For a decentralized manufacturing network, the clinics are divided into clusters using the k-means clustering method (Likas, Vlassis, & J. Verbeek, 2003). The regional hub model divides the treatment centers into 2 clusters corresponding to each manufacturing facility, while the decentralized model divides the treatment centers into 10 clusters. Within each cluster, the location of the manufacturing facility is determined as the demand weighted geometric center for each cluster. The locations of the manufacturing and treatment facilities calculated in the study are presented in Figure 3.9. The production capacity of the factory is determined to be the sum of the demand of all treatment centers within the cluster.

Figure 3.9 Locations of the manufacturing and treatment facilities determined in the study

The manufacturing cost from each manufacturing facility is determined using the cost modeling simulation based on the production facility. The study assumes no regional differences in cost value and disease incident rate. For the logistic cost, an average $2 per miles delivery cost based on ultra cold train truck delivery cost estimation is used for the calculation. The total distance traveled per batch is approximated by the round trip geometric distance between the treatment facility and manufacturing facility times a circuity factor of 1.2 for US road (Ballou, Rahardja, & Sakai, 2002). The logistic cost is the product of average per mile delivery cost and total distance traveled for the roundtrip delivery of the CAR-T product. It is assumed that each travel carries only one CAR-T product to minimize the vein-to-vein time for CAR-T treatment.

Based on the methodology described above, the network simulation model is constructed and executed to calculate the estimated COGS for the three manufacturing networks. Regional hub and centralized manufacturing have similar COGS, while the decentralized model has the highest COGS (Figure 3.10). The regional hub model has the lowest COGS at $80,271. The reduction in logistic cost for decentralized manufacturing is not enough to offset the increase in facility construction cost for building 10 facilities.

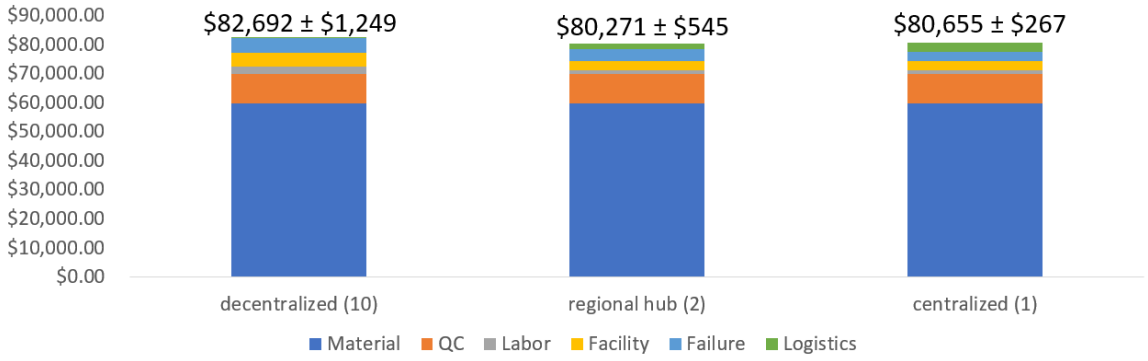

Figure 3.10 Cost comparison between three manufacturing networks

3.5 Conclusions

This chapter has provided a brief review of cell therapy cost structure, investigated the source of variations for different cost estimation studies, described the framework for cost modeling in the simulation platform, presented a benchmark for autologous CAR-T cost, and provided three case studies on how the cost module can be used to provide decision support to lower cost. The platform is a great tool for cell therapy manufacturers to improve and develop the manufacturing facility and supply chain network. A detailed case study is presented in the next chapter to showcase how the simulation platform is used to make a cost-effective design of a commercial manufacturing facility.

CHAPTER 4 COST-EFFECTIVE DESIGN OF AN ALLOGENEIC STEM CELL FACTORY FOR JOINT CARTILAGE DEFECT

In this chapter, the decision support system will be applied to design a commercial manufacturing facility for the production of a cell therapy product containing allogeneic human MSCs for the treatment of joint cartilage following the Quality by Design principle. The cell therapy product is a cartilage graft with 2 ml of biomaterial with 2.5×10^6 cells/500 μL/cm^2. The commercial facility will need to follow all cGMP standards, and the final product will need to satisfy FDA requirements with a 10-year manufacturing horizon presented in this case study.

4.1 Background

Joint cartilage defect is a common ailment that affects approximately 900,000 Americans annually, leading to more than 200,000 surgical procedures (Farr, Cole, Dhawan, Kercher, & Sherman, 2011; Merkely, Ackermann, & Lattermann, 2018). It is estimated that cartilage defects in 60-66% of knees undergo arthroscopy (Curl et al., 1997; Hjelle, Solheim, Strand, Muri, & Brittberg, 2002; Merkely et al., 2018). As joint cartilage has poor regenerative capacity and a very limited healing potential (Charalambous, 2014), it is very unlikely for damaged joint cartilage to recover its full structure, function, and mechanical properties and will gradually progress towards osteoarthritis (J A Buckwalter & Mankin, 1998; Hunziker, 2002). If left untreated, the joint can eventually become so damaged that the patient will lose the ability to walk while the pain worsens (Joseph A. Buckwalter, 2002).

Treatment for joint cartilage defect aims to control symptoms, restore joint functions and prevent long-term osteoarthritis (Detterline, Goldberg, Bach, & Cole, 2005; Doran & Young, 2013b). Current treatments include chondral debridement, a surgical procedure where the cartilage that hinders joint tissue is physically removed (Lysholm & Gillquist, 1982); marrow stimulation techniques, where a hole is drilled into the bone of the defect site so that the mesenchymal stem cell from bone marrow can bleed into and fill the defect site to restore cartilage (Kreuz et al., 2006); and whole-tissue transplantation, in which the defect tissue is excised and replaced with mature tissue from an autologous donor site or allogeneic tissue (Smith, Knutsen, & Richardson, 2005).

Another method in treating joint cartilage defects is using autologous chondrocyte implantation (ACI) to repair cartilage defects (Peterson, Minas, Brittberg, Lindahl, & Surgery, 2003). For this method, cartilage tissue is harvested surgically in a preliminary operation. The chondrocytes are then isolated from the harvested tissue and expanded in culture for 4-6 weeks. The expanded tissue is then injected into the cartilage defect through another surgery (Abelow, Guillen, & Ramos, 2006; Zhang et al., 2006). In 2016, the U.S. Food and Drug Administration (FDA) officially approved a new generation of ACI procedure called MACI (autologous cultured chondrocytes on porcine collagen membrane) for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients (US Food and Drug Administration, 2016). This is the first FDA-approved tissue-engineered autologous cell product. In a recent clinical trial report, 88% had excellent or good results with MACI, a significantly higher percentage than other treatment options (Saris et al., 2014).

Despite the numerous benefits provided by chondrocytes implantation, the procedure also came with many complications. As the process requests harvesting of donor cartilage tissue through surgery, the donor site has the possibility of becoming morbid. Also, in the case of patients with extensive cartilage degeneration, there may not be enough healthy chondrocyte population available for extraction. Lastly, during the ex vivo expansion process, chondrocytes have a high chance of becoming dedifferentiated and losing their therapeutic characteristics (Cournil-Henrionnet et al., 2008; Dell'Accio, De Bari, & Luyten, 2001; Stewart, Saunders, Burton-Wurster, & Macleod, 2000). Bone marrow-derived mesenchymal stem cells (BM-MSC) provide a good alternative option. The harvest of BM MSC does not require surgery; isolation and expansion of MSC are relatively easy. MSC can differentiate into chondrocytes and can be administered allogeneically.

BM-MSC are generally harvested through aspiration from a donor's iliac crests under regional or general anesthesia (Centeno et al., 2008; Shapiro, Kazmerchak, Heckman, Zubair, & O'Connor, 2017). These cells are also made available in commercial stem cell banks such as PromoCell. In addition, due to low expression of HLA Class I and absence of HLA Class II antigen (Le Blanc, Tammik, Rosendahl, Zetterberg, & Ringdén, 2003), MSC can be administered to patients without HLA antigen matching and thus can be manufactured allogeneically, making large-scale manufacturing and distribution possible. Several ongoing clinical trials of use MSC directly for joint cartilage defect with some evidence of cartilage recovery (Goldberg, Mitchell, Soans, Kim, & Zaidi, 2017; Lee & Wang, 2017; Simaria et al., 2013). Furthermore, MSCs have the ability to differentiate into a variety of different cell lineages, including chondrocytes, under the proper differentiation

condition (Somoza, Welter, Correa, & Caplan, 2014). Therefore, it is advantageous to combine the benefit of ease of MSC manufacturing and the therapeutic properties of chondrocytes implant.

The aim of this study is to design a commercial cell manufacturing facility that can deliver 100,000 does of cartilage graft per year worldwide through allogeneic MSC expansion and differentiation into chondrocytes. The process will be carried out in an optimized cell expansion system through quality by design principles with required purification, validation, and logistic functions that follow cGMP regulations. The proposed facility will account for 12.4% of existing and predicted cartilage defects in all OECD countries. The proposed plan can guide future stem cell manufacturer who wishes to enter the new cell and gene therapy industry.

4.2 Process flow diagram and material balance

The manufacturing process flow for the allogeneic MSC differentiated cartilage graft is detailed in Figure 4.1. Frozen MSC vials received from cell banks will first be stored in the on-site cell banking facilities. When the facility receives a production order, the vials will be thawed and plated on T75 flasks in a designated tissue culture room. After ten days, these cells will be enzymatically removed from the flask and seeded onto microcarriers within the 0.1L Vertical-Wheel Bioreactor maintained in incubators. These cells will be removed from the microcarriers and passaged into larger bioreactors every week, first to 0.5L bioreactor, then to 3L, 15L, and in the end 80L bioreactor. In the 80L bioreactor, expansion media will be switched to differentiation media to induce differentiation into chondrocytes. After differentiation, the cells will be enzymatically removed from the microcarrier and concentrated through a fluidized bed centrifuge. The

differentiated chondrocyte will be sorted from undifferentiated MSC using magnetic-activated cell sorting (MACS). The lot will then be divided into vials with 2.5×10^7 chondrocytes and filled using an automated filling machine. The vials will be frozen in a controlled rate fridge and stored in cryo and shipped to the clinic. The doctor will thaw the cells in the clinic, inject the cell suspension into the defect area and cover the suspension using a bilayer porcine collagen type I/III membrane during surgery. Expansion, differentiation, and formulation media are purchased from an outside supplier and stored in the media storage room, while phosphate-buffered saline (PBS) used in the process will be prepared in a media prep room prior to starting each batch. A more thorough acceptance quality control test and release test will be performed before expansion during the vial thawing stage and before release during the vial filling process. Sterility, viability, cell counts, surface marker, and karyotype will be tested at these stages. While simpler quality control tests such as cell count and viability test will be performed after each expansion stage during the manufacturing process. Material balance for cells and media for major unit operations on a per batch basis are shown in Table 4.1, and detailed material balance for major reagents in each stream are shown in Appendix Table A.02. In the table, streams for major unit operations are labeled in green, streams for fresh media injection are labeled in pink, streams for quality control are labeled in blue, and streams for waste treatment are labeled in yellow.

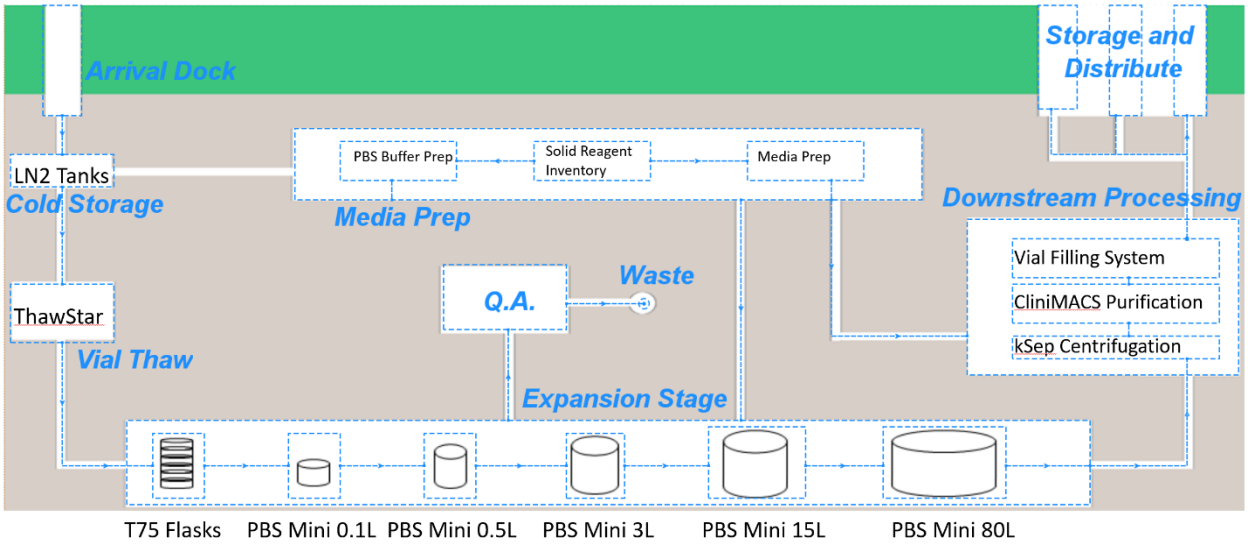

Figure 4.1 Process flow diagram for MSC production

Table 4.1 Material balances for cells and media in major unit operations per batch

	Unit Operation	Cells In	Cells Out	Volume In (L)	Volume Out (L)	Duration (days)
1	MSC Cell Thawing	2.50E+05	2.50E+05	\	0.0025	0.5
2	MSC Expansion: T75 Flask	2.50E+05	5.62E+05	0.0025	0.015	10
3	MSC Expansion: 0.1L Reactor	5.62E+05	3.63E+06	0.015	0.08	7
4	MSC Expansion: 0.5L Reactor	3.63E+06	1.56E+07	0.08	0.1	7
5	MSC Expansion: 3L Reactor	1.56E+07	1.01E+08	0.1	2	7
6	MSC Expansion 15L Reactor	1.01E+08	6.54E+08	2	10	7
7	MSC Differentiation: 80L Reactor	6.54E+08	1.58E+10	10	50	14
8	Centrifugation	1.58E+10	1.55E+10	50	0.6	0.1
9	Purification	1.55E+10	6.60E+09	0.6	2.5	0.15
10	Vial Fill	6.60E+09	6.27E+09	2.5	2.5	0.15

4.3 Process description

4.3.1 Process design using Quality by Design (QbD) principles

All processes are designed and optimized using quality by design principles to ensure compliance with cGMP standards while maintaining manufacturing efficiency and cost-effectiveness. The Quality Target Product Profile (QTPP) for the products is determined first listed below in Table 4.2. The entire manufacturing process is designed to make cure MSC manufacturing process follows the QTPP attributes listed below.

Table 4.2 QTPP attributes for MSC

Property	**Criteria**
Identity	CD105+ CD166+ CD45- CD73+ CD90+ CD80- HLA-DR- (Cournil-Henrionnet et al., 2008)
Viability	>80%
Potency	Collagen type II+ Alcian Blue+ SOX9+ COL2A1+ (Bravery et al., 2013; Ridgway, 2012)
Cell Expansion	Up to Passage 9 (Capelli et al., 2015; Ullah, Hamouda, Stich, Sittinger, & Ringe, 2012)
Doses	250,000 cells/μL/cm^2
Impurity	Endotoxin, mycoplasma, bacteria, virus, particulates free (Abou-El-Enein et al., 2013)
Karyotype	Normal
Storage	Frozen
Incubation Temperature	37 ºC for expansion, 32 ºC for differentiation (King & Miller, 2007)
CO_2 level	5% (Fekete et al., 2012)
Maximum Confluency	80% (Doran & Young, 2013a)
Minimum Glucose Concentration	1 mM (Kim & Cho, 2013)
pH level	7.22
Oxygen Level	3% (Haque, Rahman, Abu Kasim, & Alabsi, 2013)

4.3.2 Overall process description

4.3.2.1 Upstream processes

Various cell media and PBS solution will be prepared in a dedicated media preparation area. PBS will be prepared using a mixture of dry chemical consists of sodium chloride, potassium chloride, sodium phosphate, potassium phosphate, and water for injection (WFI) for a final pH of 7.22 using an established recipe for cGMP production ("Common stock solutions, buffers, and media," 2001). RoosterNourish™ MSC media from RoosterBio® will be used for MSC expansion (Fekete et al., 2012), while MesenCult™ ACF Chondrogenic Differentiation Medium will be used for the chondrogenic differentiation of MSC (Solchaga, Penick, & Welter, 2011). These media are standardized, xeno-free, cGMP compliant with little batch-to-batch variation.

4.3.2.2 Cell banking & vial thaw

MSC cells will be purchased from a cGMP-compliant commercial stem cell bank. Stem cell donors will underwent strict health history and infectious disease screening, required by the Food and Drug Administration, American Association of Blood Banks, and Foundation for the Accreditation of Cellular Therapy (Alsuhaibani et al., 2015; Tomblyn et al., 2009). As one batch of MSC can be made into 2,500 doses. It is critical that MSC donor is of optimal health and free of any infectious disease. After arriving at the manufacturing facility, cells will be stored in a VWR® CryoPro® Liquid Nitrogen Cell Storage Tank, which is capable of holding a maximum of 875 vials larger than 500 vials/tank requirement. The tank will be refilled with liquid nitrogen every two weeks. When a production order is received, a vial will be removed from the storage and thawed with Astero® Thawstar® CFT2 Cell Thawing System. The cell thawing system has a

cGMP compliant standardized thawing procedure that is reproducible and leads to higher cell recovery and less variability between batches.

4.3.2.3 Cell expansion & differentiation

MSC from vials will be expanded from passage 4 to passage 9 in a series of bioreactor trains. 5% of the cells will be taken from the vial initially to check for its viability, sterility, and density. After passing the acceptance check, the MSC will be first expanded in the T75 vial flask for 10 days until reaching 80% confluency(Fekete et al., 2012; Lawson et al., 2017). The MSC cells will be subsequently grown in PBS Mini 0.1, 0.5, 3, 15, 80 with microcarriers for each cell passage at 37 ºC and 5% CO_2. There will be two full-volume media exchanges during the cultural duration for T75 Flasks and two half-volume for each bioreactor.

For each scale-up process, the adherent MSC cells will be detached using a xeno-free trypsinization reagent TrypLE™ following the standard detachment protocol from the reagent manufacturer. The cells will first be rinsed with PBS and incubated with the trypsinization reagent before switching out with growth media and transfer into a new bioreactor. After a week of expansion in the PBS Mini 80 reactor, the expansion media will be switched to differentiation media to initiate the differentiation of MSC into chondrocyte.

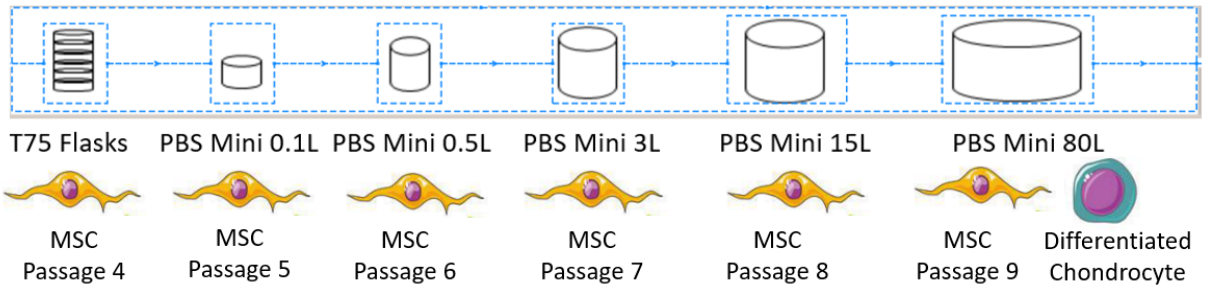

Figure 4.2 MSC expansion and differentiation process

4.3.2.4 Purification

The differentiated cells are first concentrated using the kSep centrifugation system to remove microcarrier, waste, extracellular matrix, and other cellular secretions. Chondrogenic differentiated MSC cells will then be sorted out from undifferentiated cells using magnetic-activated sorting techniques (MACS) by CliniMACS machine. The yields of the MACS process will be about 60%, with a processing time of three hours (Miltenyi, Müller, Weichel, & Radbruch, 1990). Compared to undifferentiated MSC cells, differentiated cells will have reduced expression of surface markers of CD44, CD73, CD90, CD105, and CD166 (Ullah et al., 2012). Chondrocytes can then be isolated through negative selection with the chondrocytes eluted in the media. The CliniMACS machine has been approved for use in the cGMP manufacturing process.

4.3.2.5 Inactivation

Viral inactivation is a critical step in the traditional monoclonal antibody (mAb) biomanufacturing process to ensure product safety. Common viral inactivation techniques involve filtering, solvent/detergent treatment, low pH inactivation, heating, and

chromatography (Clutterbuck et al., 2017). However, since the final product is comprised of living cells, all these techniques would reduce cell viability and become unfeasible (Schnitzler et al., 2016). Strict quality control and monitoring system are implemented throughout the manufacturing process for virus detection. All reagents and starting material will require FDA approval for sterility (Giancola, Bonfini, & Iacone, 2012). As all the equipment used in the process are closed and fully automated, the manufacturing will take place in a Class C cleanroom with equipment placed in isolators to prevent contamination from surroundings (Lopes et al., 2018). WFI used for media preparation will also be purified according to cGMP protocol to remove all viruses.

4.3.2.6 Preparation for shipping

Purified chondrocytes will be filled into individual cryovials using the standard procedure from the fill-it Vial Filling System from TAP Biosystem. The system can fill 96 vials in less than one minute and can minimize exposure to DMSO and reduce variability between vials. 2.6 hours are required to fill up to 250 vials.

After vials are filled, the products will be put in a controlled-rate freezer to freeze the vial to recommended -120 ºC for cell storage (Li & Ma, 2012). Vials will also be labeled using a designated barcode system that allows tracking throughout the entire process.

4.3.2.7 Quality control test

Quality control tests will be performed based on strict FDA regulations on human cells, tissues, or cellular and tissue-based products (HCT/Ps) (Food and Drug Administration, 2008; Food and Drug Admins-CBER, 2014). The quality tests required for the process are listed in Table 4.3.

Table 4.3 List of quality control tests

Test Attribute	Equipment
Cell Density	Particle Counter
Viability	Trypsin Blue
Identity	Flow Cytometer, qPCR
Sterility	Blood Culture Media Test
Karyotype	Karyotype Test Kit
Mycoplasma	Plate Reader
Endotoxin	Endotoxin Test Kit
Residual Virus	qPCR
Potency	Alcian Blue and Type II Collagen Dye

4.3.2.8 Acceptance check

Cells thawed from the cell bank will first go through an acceptance check to ensure the cells are up to standard for expansion. The cells will be checked for density, sterility, and identity. Flow cytometry will be used to check for the identity and purity of MSC cells according to the test criteria detailed in the previous section.

4.3.2.9 In-process check

Samples from cells during the expansion stage will be taken out and tested for cell counts and identity using a multisizer and flow cytometer to monitor its growth and differentiation status.

4.3.2.10 Release check

Before the cells are released, the product will undergo a list of sterility tests, including sterility culture, mycoplasma, endotoxin, and vesicular stomatitis virus (VSV-g) to ensure its safety (National Academies, 2017; Scott, Schachtele; Christine, Clouser; Joy, 2013). The identity and potency of chondrocytes will also be checked from both its surface

cell marker using a flow cytometer as well as a more definitive qPCR test. Only the vials that pass all tests will be cryogenically stored and sent to the medical facility.

4.3.2.11 Storage and shipment

The frozen vial will be kept in the CryoPort cryogenic storage system awaiting shipment orders. These cryogenic vials will be shipped by a specialized biologics shipper using SmartPAK II Condition System that allows real-time monitoring and tracking throughout the entire delivery process to ensure cells arrive at the clinics under the optimal condition.

4.3.2.12 Supply chain

Stock levels of critical reagents are being monitored using the manufacturing modeling software designed for this facility. A periodic review product policy is implemented to minimize the chance of backorder and reduce the impact of a potential supply chain disruption scenario (Bossert & Willems, 2007). According to the simulation model, the current implementation of a weekly reordering schedule can successfully mitigate a volatile product demand (Figure 4.3).

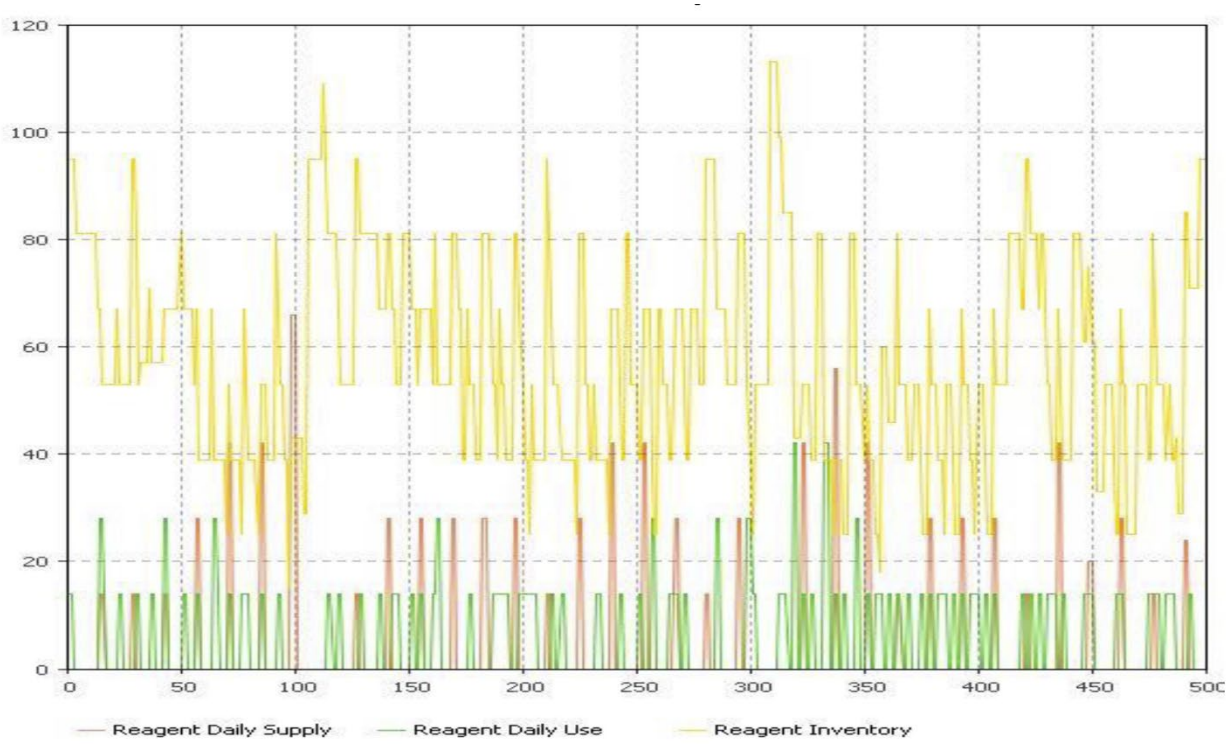

Figure 4.3 Inventory management for critical reagent using weekly periodic review

4.3.2.13 Waste management

All consumables, including equipment components, used media, and other reagents, will be autoclaved before disposal. Media that are not yet disposed of will be temporarily stored in a stainless-steel waste tank before being autoclaved and disposed of into the sewer system. The autoclave process will be performed once a day.

4.4 Energy balance and utility requirement

Energy and utility use calculation is performed using the processing modeling software developed for the manufacturing process based on a production capacity of 100,000 items per year. Cost for electricity, gas and heat, sewer treatment, and water is based on industrial utility for the state of Pennsylvania, the site of the production facility

(Pennsylvania Scorecard, n.d.; Priddy, n.d.). The electricity usage is estimated from the equipment specification sheet and follows the calculation used for the industrial cost report analysis of two GMP Cell therapy product facilities, the Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany, and the University of California Davis GMP facility in Sacramento, California, the United States (Abou-El-Enein et al., 2013) The total yearly cost for utilities is estimated to be about $66,093 which is around $0.66 for each treatment dose given the 100,000 dosages per year production capacity.

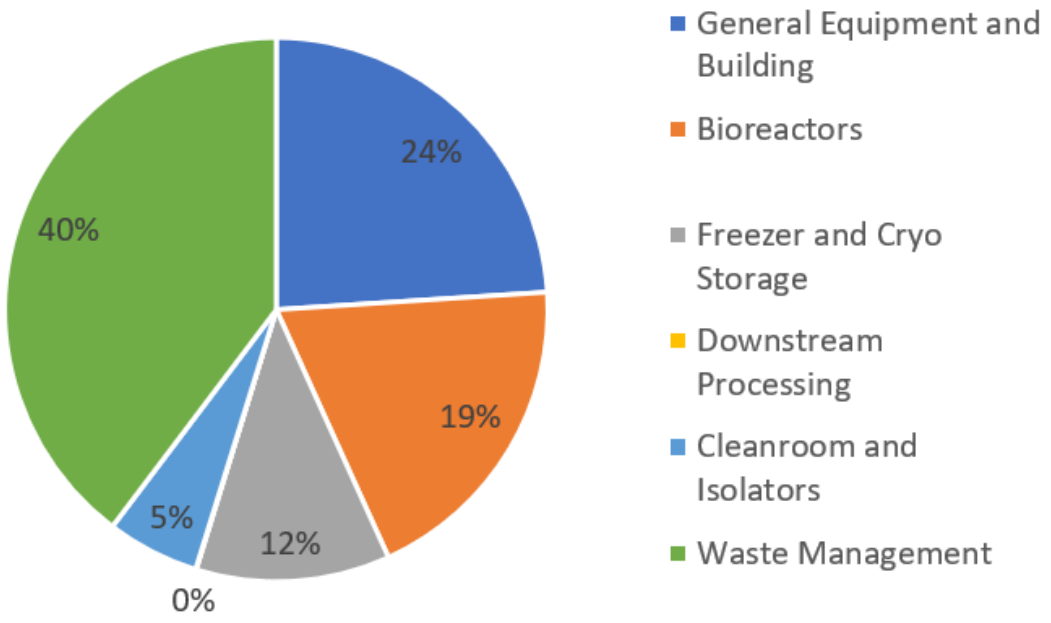

Figure 4.4 Percent of electricity use per year for major operations

Table 4.4 Total utility cost per year and per good based on 100,000 items/year

	Units (kWh)	Cost/Unit (USD)	Yearly Cost	Cost per Good
Electricity (kWh)	890479	0.0692	$ 61,621.15	$ 0.62
Gas and heat (MMBTU)	284	13.98	$ 3,970.32	$ 0.04
Sewer (1000 gallon)	73	5	$ 365.00	$ 0.00
Water (1000 gallon)	67	2.04	$ 136.68	$ 0.00
Total			$ 66,093.15	$ 0.66

4.4.1 Equipment cost summary

The total purchased equipment cost is 1.72 Million USD for the first year, with the scale-up of operation each year. By year 4, the total equipment cost will reach 4.4 Million USD (Figure 4.5). A detailed list of all equipment used in the manufacturing facility can be found in Appendix Table A.03. Equipment for major unit operations such as cell culture, purification, and isolation accounts for 70% of the equipment cost. The price is consistent with the cost analysis research conducted on other similar cell therapy factories by Lopes *et al.*, in which they calculated the equipment cost of their cell therapy factory at 2.45 Million USD to produce 260 batches a year (Lopes et al., 2018). While the factory at year 4 will produce 400 batches a year at 4.4 Million USD.

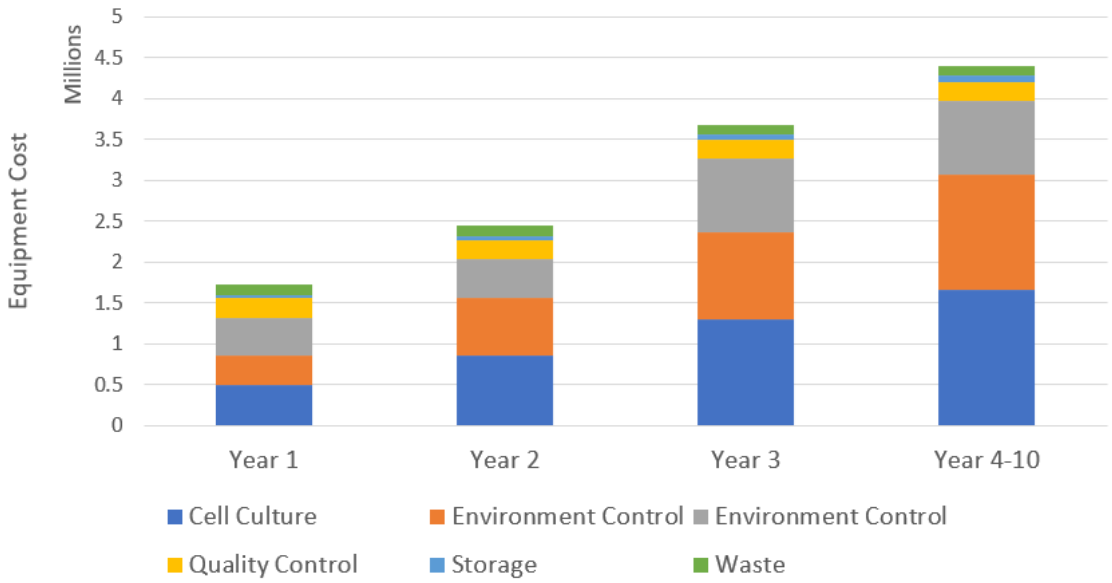

Figure 4.5 Total equipment purchase cost breakdown by category for each year

4.4.2 Fixed capital investment summary

Using the estimation method outlined in the Bioprocess textbook (Petrides, 2013), shown in Table 4.5, the fixed capital cost can be estimated by adding total plant direct cost, total plant indirect cost, with a multiplier for contractor's fee and contingency. As cell therapy product manufacturing is a nascent industry with very strict federal regulation and oversight, the highest multiplier is used to estimate the fixed capital cost. As shown in Table 4.6, the total fixed capital is calculated to be around $61.58 Million.

Table 4.5 Fixed capital cost estimation heuristic adapted from "Bioprocess Design and Economics" (Petrides, 2013)

Cost item	Average multiplier	Range of multiplier values
Total plant direct cost (TPDC)		
Equipment purchase cost (PC)		
Installation	0.50 × PC	0.2–1.5
Process piping	0.40 × PC	0.3–0.6
Instrumentation	0.35 × PC	0.2–0.6
Insulation	0.03 × PC	0.01–0.05
Electrical	0.15 × PC	0.1–0.2
Buildings	0.45 × PC	0.1–3.0
Yard improvement	0.15 × PC	0.05–0.2
Auxiliary facilities	0.50 × PC	0.2–1.0
Total plant indirect cost (TPIC)		
Engineering	0.25 × TPDC	0.2–0.3
Construction	0.35 × TPDC	0.3–0.4
Total plant cost (TPC)	TPDC + TPIC	
Contractor's fee	0.05 × TPC	0.03–0.08
Contingency	0.10 × TPC	0.07–0.15
Direct fixed capital (DFC)	TPC + Contractor's fee and contingency	

Table 4.6 Breakdown of capital cost

Equipment Purchase Cost	$	4,405,303
Total Plant Direct Cost	$	31,497,916
Total Plant Indirect Cost	$	22,048,542
Total Plant Cost	$	53,546,458
Total Fixed Capital	$	61,578,427

4.5 Analytical approach, product safety, and efficacy

The QTPP of the final product and the list of quality control items have been addressed in the above sections. All the specifications will be satisfied to ensure the safety and efficacy of the products. The testing procedure can be categorized into starting material,

intermediate and final product test (Fekete et al., 2012), as shown in Figure 4.6. In the beginning, the sterility and impurity of source human cells/tissues and other process consumables will be tested. Also, cytokine analysis will be performed to quantify human cytokines and chemokines. During and after cell cultivation, the CO_2, pH, glucose, and oxygen level will be real-time monitored. For each three to four days, the supernatant samples will be collected for sterility, impurity, and cytokines monitoring. After cultivation and purification, the cell sample will be collected to perform all the basic testing mention above; in addition, the cell density, karyotype, and potency will be verified to ensure all the designed CQA specifications are fulfilled. Finally, the final product will be cryopreserved and shipped to the patient when needed. A basic sterility and impurity test will be performed right before the treatment.

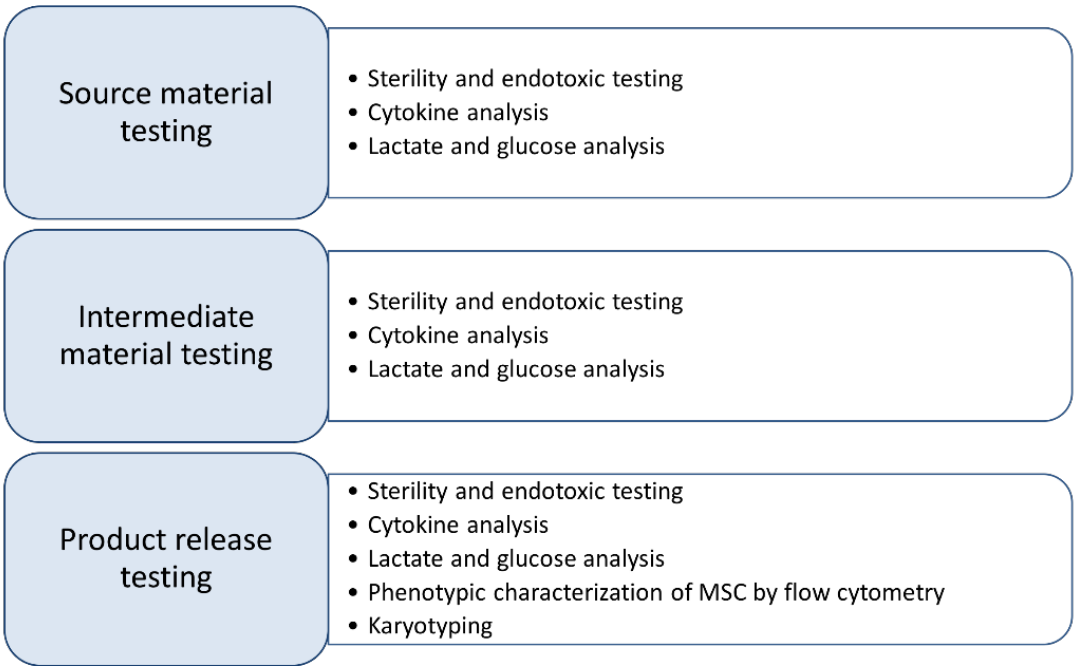

Figure 4.6 Categories of critical quality attribute testing

4.5.1 Manufacturing safety

The manufacturing process safety includes two major aspects, staff and environment. The process steps will be performed by qualified personnel. According to the Code of Federal Regulation (CFR) (U.S. Food and Drug Administration, 2020a), all personnel must be clear about the potential hazards of their work, and they must be well trained to have enough knowledge and capability to perform their assignment safely. In addition, for each process step, standard operating procedures (SOP) will be established and updated to reduce the risk of exposing contaminated human cells or tissue to staff or the environment. These SOPs will be accessible to all related personnel (U.S. Food and Drug Administration, 2020b).

Incoming reagents, bio-materials, and process consumables will be sterilized and verified to meet CGTP specifications (U.S. Food and Drug Administration, 2020e). Upon arrival, in-house sterilization and test procedure will be performed to ensure the safety of staff and product. While processing human cells or tissues, each material should be clearly labeled and must not be mixed. For every reagent or process material, the date of receipt, quantity, purpose, storage, usage, date of expiration, and the material test result will be recorded and properly stored for at least 3 years.

The equipment chose in the manufacturing process is compliant with cGMP regulation and certified by FDA. According to CFR (U.S. Food and Drug Administration, 2020d), the construction, electronics, mechanical, and operation mechanism should be well designed to prevent disease or contaminated material exposure to staff and workplace. During operation, each piece of equipment will be regularly monitored, calibrated, and

maintained to prevent unexpected problems. All the equipment condition and maintenance records will be documented and retained for 3 years.

During the manufacturing process, the environmental condition of the working space will be real-time monitored to ensure all equipment and process are operating under appropriate conditions, thus preventing unexpected contamination or exposure of communicable disease agents (U.S. Food and Drug Administration, 2020c). Typical environmental conditions include temperature, humidity, pressure, ventilation, and air filtration. The sensor and monitoring system will be checked repeatedly.

4.6 Economic analysis

4.6.1 Manufacturing cost

Manufacturing costs include materials (cells, media, reagents), consumables (bags, tubes, flasks, bottles, …), labor (operators, supervisors, quality), capital depreciation (facility and equipment), distribution, and utility (electricity, waste, maintenance). Labor consists of operations with 3 personnel per clean room, including 2 operators and 1 supervisor and 3 quality with 2 quality control and 1 quality assurance (Lopes et al., 2018). A 10% failure rate is assumed per batch. The cost breakdown is shown in Figure 4.7. The first-year cost is estimated at $136 million and ramped up to $277 million to year 4. Cost per batch starts at $110 thousand and comes down to $70 thousand as manufacturing gradually scaled up. Since one batch can produce 250 doses in the model, the cost per dose is only $542 at the beginning and came down to $276 by year 4 (Table 4.7). This cost is currently lower than the cost of many other allogeneic cell therapy products from literature since the cell dosage required for this treatment (~25 million cells) are much lower than

other MSC products (~100 million cells). (Abbasalizadeh, Pakzad, Cabral, & Baharvand, 2017; Hassan et al., 2015; M. J. Jenkins & Farid, 2018). The reduced cell dosage can lower treatment cost considerably, and the calculated cost per batch is consistent with estimations from other peer-reviewed cost analysis journal articles.

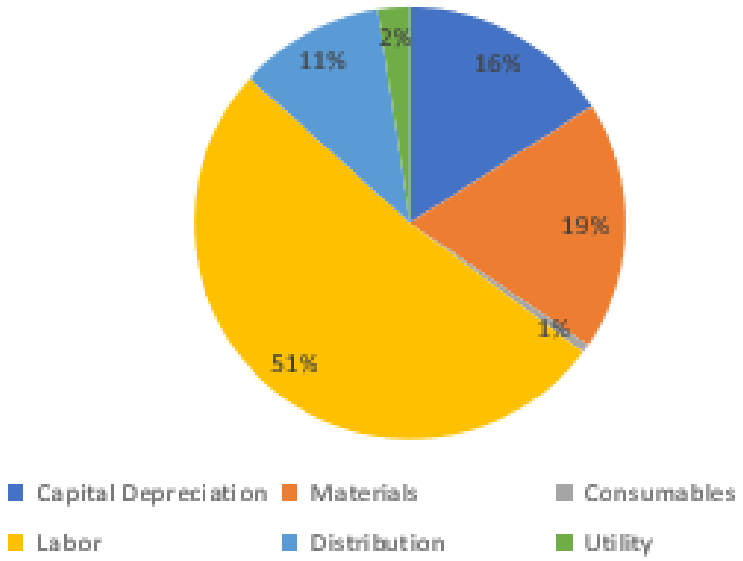

Figure 4.7 Pie chart of cost breakdown for year 4–10

Table 4.7 Manufacturing cost per year, per batch, and per dose

	Year 1	**Year 2**	**Year 3**	**Year 4-10**
Yearly Cost	$13,559,728	$15,907,836	$25,346,063	$27,651,258
Cost per Batch	$112,998	$72,308	$ 81,761	$70,901
Cost per Dose	$ 542	$ 318	$338	$276

4.6.2 Financial analysis

To account for expenses in R & D as well as sales and marketing expenses, the selling price is determined so that COGS account for 15% of the total sale. The 15% target is determined based on the industrial standard for biologic manufacturing and allogenic cell therapy manufacturing (M. J. Jenkins & Farid, 2018). For autologous cell therapy, COGS usually account for a much larger percentage of the total sale (Lipsitz et al., 2017; Spink & Steinsapir, 2018). Based on a COGS of $276 per dose, the drug is set to be $1,840 per treatment. The MACI treatment price for joint cartilage damage is $14,083. The unit cost of mosaicplasty is $2,639, and the unit cost of microfracture is $1,405. This price is 85% cheaper than the best treatment available, and this treatment has a much shorter and easier recovery period compared to microfracture, which usually requires the patient to be on crutches for four to six weeks after the surgery (Steadman et al., 2003). Given the size of the market, the selling price will generate annual revenue of $46 M in year 1 and rises to $184 M in year 4. This will result in a gross profit of $32.5 M in year 1 and rises to $156.4 M in year 4. The investment in building the factory will be paid back within 2 years. However, R & D, clinical trial, and other operating costs, including administrative and sales & marketing cost, are not included, and these items also represent significant capital investment and operating costs that are not captured from this analysis.

4.7 Conclusions and recommendations

This case study demonstrated how the simulation framework can examine and compare different process configurations and choose a process design that delivers a quality product with commercial viability. The case study has demonstrated the robustness of the design by examining the project from various angles and has performed both

economic and technical reviews from analyzing the technical and market aspects of existing products. The report includes analysis on equipment selection, material balance, facility design, economic feasibility, as well as compliance with regulatory requirements, including quality control methods and facility layout. The proposed process incorporates various design options that meet the overall goal of designing an ethically sound, high quality, and commercially competitive product.

In order to truly realize the proposed commercial process, further validation of the simulation result will need to be validated. Hosts of thorough and comprehensive experiments and assays need to be conducted to evaluate the effectiveness of the product and verify the optimized equipment setup described in the case study. Investors and developers should also monitor closely any recent development in biotechnology and manufacturing science to evaluate and incorporate new technologies to improve the current design or update the timeline and cost of the facilities according to more recent scientific and industry studies.

CHAPTER 5 RISK ANALYSIS AND MITIGATION FOR CELL THERAPY INDUSTRY – A CASE STUDY

5.1 Background

COVID-19 pandemic has wreaked great havoc on the pharmaceutical industry. Trade restrictions (U.S. Senate Republican Policy Committee 2020) and sudden surges in demand for many medical supplies used to treat COVID-19 or manufacture vaccines have led to a worldwide shortage of pharmaceuticals, critical raw materials, reagents, and other medical supplies (Shih, 2020). Travel restrictions and social distancing measures have also created staffing shortages for many pharmaceutical manufacturing plants and healthcare facilities. As of October 2020, 43% of acute care medicines such as antibiotics, blood thinners, and sedatives are in short supply (Silverman, 2020). These shortages have continuously worsened as the rate of new COVID-19 cases kept climbing throughout the initial year of the pandemic (Schondelmeyer et al., 2020). Within the pharmaceutical industry as a whole, cell therapy manufacturing institutions and companies are facing especially severe disruptions due to their complex manufacturing supply chains. Border closures and travel bans have prevented patients' cells from reaching manufacturing facilities. Some products that would have been delivered fresh have had to be cryopreserved. Hospitals have pushed back cell therapy treatments and clinical trials to reserve ICU spaces for COVID-19 patients (Boodman, 2020). Production capacities for many contract manufacturing facilities have also been affected due to their commitments to vaccines and ancillary reagent manufacturing for COVID-19 (Stanton, 2020). Many skilled operators within these facilities have also been recruited and diverted for vaccine

and reagent manufacturing, causing further shortages within the cell therapy industry (Koh, 2021). A recent McKinsey & Company survey has shown that one-third of cell therapy companies reported manufacturing delays or complete shutdowns, and one in five reported problems with the procurement of supplies (Loche, Mossmann, Van der Veken, & Yang, 2020).

Cell therapy is a fast-growing emerging industry with great potential for treating fatal and life-debilitating ailments, including cancer, genetic, and neurodegenerative diseases, that can often lead to remarkable clinical outcomes. An example of a more recent cell therapy product, CARTITUDE-1, from Janssen and Legend Biotech, reported a 95% remission rate for clinical trial participants with relapsed or refractory multiple myeloma (Madduri et al., 2020). As of February 2021, 19 cell therapy products have been approved by the US FDA, according to the official agency website (U.S. Food and Drug Administration, 2021). By 2025, it is estimated that 10–20 cell therapy products will be approved every year (Gottlieb & Marks, 2019). However, the use of live cells and tissues has also created additional challenges and vulnerabilities for the manufacturing and logistics of cell therapy compared to other pharmaceutical products.

The manufacturing process begins by collecting immune cells from the patient or a donor at a collection facility. The cells are then transported to a manufacturing facility for processing. Following manufacturing, quality control testing, and quality assurance review, the final drug product is transported to the treatment facility, where it is administered to the patient (Figure 5.1). The entire process includes numerous hand-off points where the chain of custody must be maintained. The complexities of donor sourcing and transport live cells, reagents, consumables, and other medical supplies between manufacturing and

administration share many similarities with organ and tissue transplantation. The large-scale standardized pharmaceutical manufacturing process combined with a supply chain as complex as that of organ transplantation makes managing the cell therapy manufacturing and supply chain uniquely challenging compared to traditional pharmaceutical manufacturing.

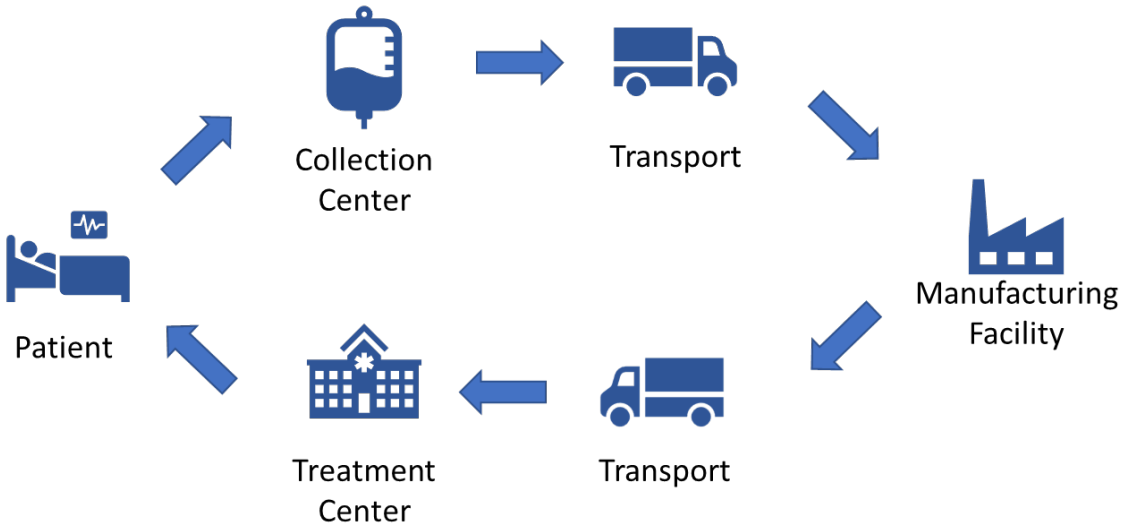

Figure 5.1 Illustration of a typical autologous cell therapy supply chain depicting the journey of the cell therapy product

The cell therapy industry is a new and relatively small player in the biopharmaceutical industry as a whole. Most manufacturers rely on sole suppliers for highly specialized critical reagents, making the manufacturers vulnerable to any supply chain disruption (Wang et al., 2019). The supply chain is even more vulnerable for autologous cell therapy manufacturers, where a patient's own cells are collected as the raw material for the patient's cell therapy product. During the first peak of the COVID-19 pandemic in spring 2020, many blood collection centers either completely stopped

operations or severely reduced their operating time to protect the health of the blood donors and to divert many of the healthcare workers who collect blood to fight the pandemic (Boodman, 2020). The availability of manufacturing and quality testing personnel has also been affected similarly. Stay-at-home orders, social distancing measures, infections and the quarantine of staff members, lack of personal protective equipment (PPE), diversion of key personnel to manufacture COVID-19 related therapeutics and vaccines, and now the administration of vaccines have all contributed to staff shortages (Koh, 2021; Loche et al., 2020). These procurement and staffing challenges have led to delays or halts in the cell therapy manufacturing process during the spring 2020 peak. Even though many of the manufacturing facilities and collection centers recovered to varying extents from the initial shock, there are still many lingering disruption impacts with each subsequent wave. The system remains vulnerable to the resurgence of COVID-19 variants or the emergence of a new infectious agent in the future. A list of potential sources of supply chain disruptions for the cell therapy industry is presented in Table 5.1. Many cell therapy products are used on critical patients with limited prognoses, and the products themselves are living cells that can deteriorate over time if not properly stored or cryopreserved. A delay in manufacturing and a rejection of a final drug product for administration will leave patients with progressing disease more vulnerable and increase patient adverse outcomes.

Table 5.1 Sources of risks and disruptions in cell therapy manufacturing

Supplier Side	**Manufacturing Side**	**Hospital Side**
Shipping delays and halts	Lack of PPE	Lack of ICU beds
Border closures; canceled flights for donors	Social distancing and quarantine of essential personnel	Shortage of drug supply to treat side effects
Shortage of reagents	Delays in service and repair of equipment	Travel restrictions for patients
Failure of regulatory inspections	Failure of regulatory inspections	Lack of hospital staff

There are many "resilience" strategies that cell therapy companies can explore to reduce the risk of supply chain disruption and mitigate their impact (Table 5.2). Companies can prepare for such eventualities before a disruption occurs by cross-training staff that can substitute unavailable key manufacturing personnel and additional buffer stock for reagents. Companies can also seek additional suppliers for critical reagents and transship orders from other facilities in different geographical locations less impacted or not impacted by the disruption. After the disruption has started, companies can also explore different priority and triaging policies by prioritizing or even rejecting some of the orders.

Table 5.2 The common types of resilience and mitigation strategies and the relative cost associated with implementing these policies

Mitigate Impact (low implementation cost)	**Increase Preparedness** (medium implementation cost)	**Build Resilience** (high implementation cost)
Priority Queueing/Rationing: Develop criteria for rationing Prioritize urgent care cases	*Scenario Planning:* Simulate what-if scenarios Identify bottlenecks & vulnerabilities	*Build Redundancy:* Increase inventory Extra bioreactor Cross-train staff Extra supplier
Demand Shaping: Estimate production capacity Proactively determine treatment criteria	*Emergency Plans:* Develop emergency protocols Have a clear chain of command	*Build Flexibility:* Multi-skilled operators Reagent transshipment

An agent-based computational simulation model can be a useful tool to help understand the effect of such disruptions on supply chain operations and patient access. Such a model can also be used as a decision support tool to determine the best resilience strategies for cell therapy manufacturers to minimize the impact of such disruptions. A simulation model can provide an information-rich view in a user-friendly interface for cell therapy manufacturers and other relevant stakeholders to intuitively plan different disruption scenarios customized to the precise configuration of their manufacturing facility. A simulation model can also capture many of the complex interactions between patients, cell specimens, reagents, operators, and equipment that traditional mathematical modeling may fail to take into consideration accurately.

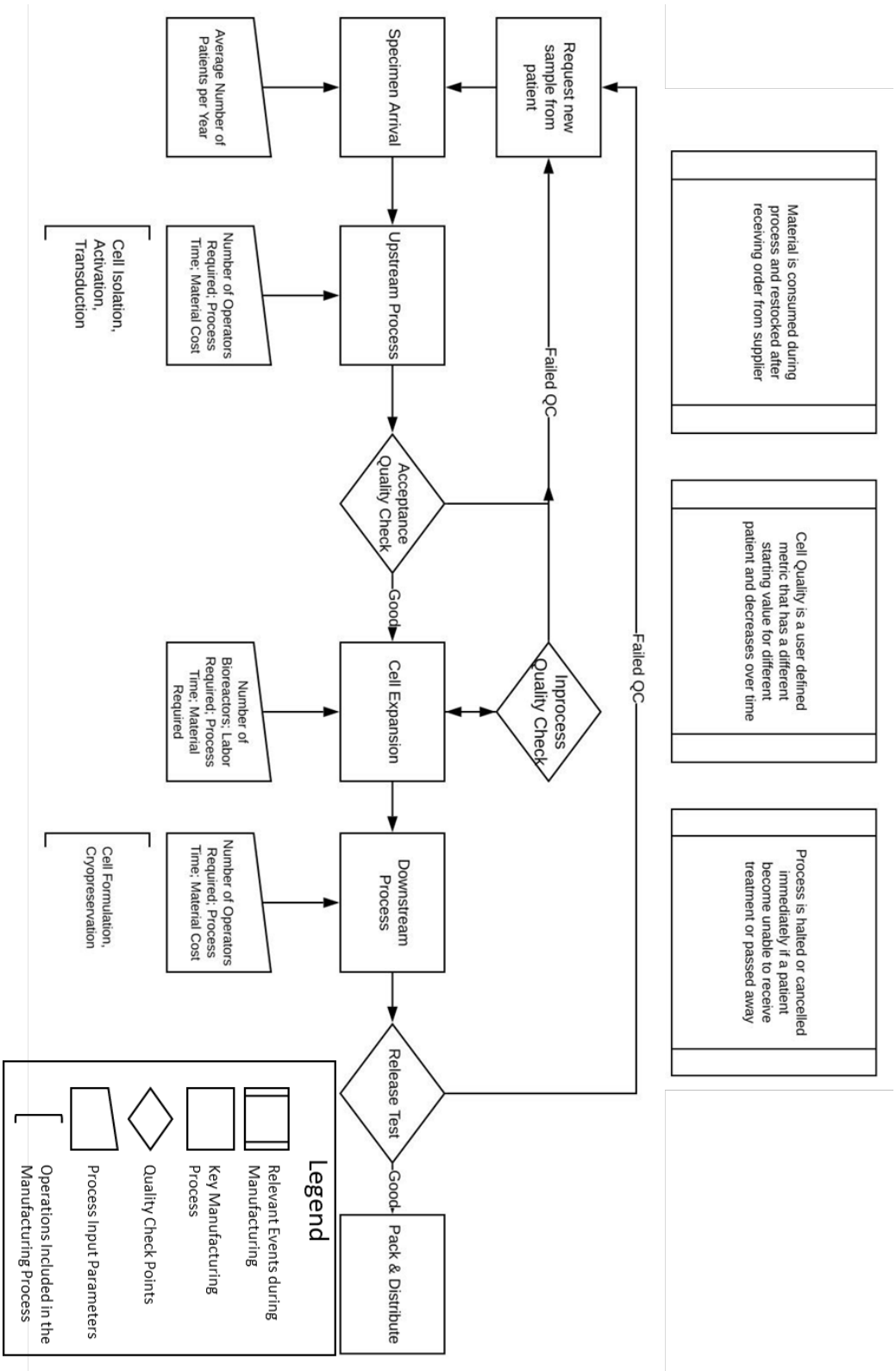

Figure 5.2 Layout and logic of the simulated manufacturing process in the modeling software

For the research presented here, the agent-based simulation model described in **Chapter 2** is customized for risk analysis and mitigation for studying the impact of disruptions on the cell therapy industry. In particular, this chapter examines the impact of prolonged reductions in the availability of reagents and operators caused by the COVID-19 pandemic on manufacturing performance and patient access. The chapter also investigates how incorporating redundancy into production and reagent inventory while implementing a priority policy for the sickest patients during the disruption can help mitigate the negative impact of such disruptions. The effectiveness of the patient priority policy is also compared to that of the typical first-come, first-serve scheduling rule. Using the information from these simulations, mitigation strategies applicable to cell therapy manufacturers can be proposed and prioritized to prepare for COVID-19 and other future pandemics and disruption events.

5.2 Methods

Using the agent-based simulation model developed and described in **Chapter 2** (Wang et al., 2019), this study investigates how a reduction in operator and reagent availability can impact the patients' adverse outcome rate, suggesting a method to reduce the impact of the disruption. Reagent availability is defined as the amount of reagent supply available to order from the supplier weekly. Operator availability is defined as the number of operators directly involved with the production process available in one shift. Both the reagent and operator availability are measured against a perfectly lean manufacturing setup with zero redundancy.

For the reagents, this study implements a periodic-review base-stock inventory policy. For this policy, an order for reagent replenishment is placed every week to bring

the inventory position up to the base stock level S. It is assumed that an order will take a week to arrive at the facility. The base stock level is the sum of the average demand μ during the review period D and delivery period L, and the standard deviation of demand σ multiplied by a safety factor k. The safety factor determines how likely the inventory will experience a stockout. A safety factor of 3 corresponds to a 0.03% chance of a stockout event, and a safety factor of 6 corresponds to a 3 in a million chance of having a stockout event. Thus,

$$S = \mu_{D+L} + k\sigma_{D+L}$$

During the disruption, delivery capacity or the amount of reagent available to purchase from the supplier will be limited for each order. The factory will not be able to order up to the base stock level if the difference between the current inventory level and the base stock level is larger than the delivery capacity. Reagent availability measures the delivery capacity during the disruption. 100% reagent availability means the amount of reagent supply available to order from the supplier is equal to or greater than the average amount of reagent needed during the same period.

For the operator, 100% operator availability means the number of available operators in a single shift is at least as great as the minimum number of full-time-equivalent (FTE) operators required in a shift based on labor hour calculation. The minimum number of operators is calculated by dividing the total labor hours required to meet demand over the time period by the number of working hours per operator. A facility with an annual production capacity of 5,000 batches will require an average of 520.5 labor hours to meet the average demand in a 12-hour shift, requiring at least 44 operators to cover. Thus, a factory with 50 operators in a shift corresponds to an operator availability of 50/44 =

113.6%. A list with the minimum number of operators required per shift is included in Table 5.3.

Table 5.3 The minimum number of operators required per shift to fulfill production orders in a perfectly lean system based on labor hour calculation

Annual Production Capacity	**Minimum Operators Required per Shift**
250	4
1,500	14
5,000	44

In reality, a perfect lean system is unsustainable since having only the capacity to meet the average demand means the facility will be unable to meet the demand 50% of the time when the actual demand is larger than average. It is also improbable for an operator to schedule the production process with zero wait time or downtime in between orders. Therefore, all manufacturing facilities in a normal setting must operate with some redundancy above 100% availability to account for stochasticity and scheduling limitations.

The adverse outcome includes patient mortality during treatment or disease progression beyond the capability of the treatment. Lack of clinical staff or ICU beds during the pandemic peak can also contribute to the adverse outcome of a patient unable to get treated. The study set the length of the disruption to 6 months and 12 months with varying degrees of severity from a full disruption to a partial disruption to test whether the manufacturing facility can reach a new steady state in manufacturing capability under a prolonged disruption. Both the number of operators in a shift and the maximum number of

units of reagents allowed for purchase in one order are reduced during the disruption. The study also tested different disruption scenarios on manufacturing facilities of different sizes: an academic manufacturing facility capable of making 250 batches a year, a midsize factory making 1,500 batches a year, and a large factory making 5,000 batches a year.

To understand how redundancy affects the impact of disruption, the study varied baseline labor and utilization and base stock level to investigate how much manufacturing delay and the patient adverse outcome can be reduced by increasing the number of operators and reagent inventory during normal operations. A list of parameters and assumptions used in the simulation platform is shown in Table 5.4.

Table 5.4 List of input parameters and assumptions used in the simulation model. Bioreactor numbers are in great excess to remove any impacts caused by potential bioreactor shortages

Parameter	**Baseline Value**	**Treatment in the Case Study**
Patient Daily Adverse Outcome Chance	0.3%	Fixed
Viability of Final Cell Products	80%	Fixed
Tissue Contamination Probability During Sampling	0.2%	Fixed
No. of Bioreactors	100	Fixed
Bioreactor Failure Rate	1%	Fixed
Bioreactor Repair Time (day)	5	Fixed
Reagent Delivery Frequency (day)	7	Fixed
Delivery Lead Time	7	Fixed
Patients per Year	250 | 1,500 | 5,000	Variated
Base Stock Level Safety Factor	0 | 3 | 6	Variated
Disruption Length (month)	6 | 12	Variated

During normal operations, the manufacturing facility is assumed to have a first-in-first-out policy (FIFO), where the order of the manufacturing requests is solely determined by the order arrival time. However, during the disruption where the manufacturing capability is limited, the study also investigated whether assigning urgent critical patients ahead of regular patients will improve the overall patient adverse outcome without potentially worsening the condition of regular patients. The order of all urgent patients' requests and regular patients' requests are serviced FIFO within each patient category. This admittance policy will be referred to as the priority queueing policy (PQ). A reduction in adverse outcome rate is calculated by comparing the difference in patient adverse outcome rate with a facility using the FIFO policy and the PQ policy under the same disruption parameters. The list of parameters used in the PQ study is listed in Table 5.5.

Table 5.5 Parameters used for priority queueing policy study

Regular Patient Daily Adverse Outcome Probability	0.003
Urgent Patient Daily Adverse Outcome Probability	0.02
Initial Proportion of Urgent Patient	0.1
Probability of Regular Patient Become Urgent Each Day	0.01

Each 3-dimensional surface plot generated in the Results section was determined by varying both operator and reagent availability and generated with 10,000 simulation experiments. Each line in the 2-dimensional line plot in the Results section was determined by varying either operator or reagent availability to generate 5,000 experiments. The

number of experiments was chosen to reduce the effect of the randomness of the stochastic simulation model. A list of definitions of terms used in the study is shown in Table 5.6.

Table 5.6 A list of definitions for the terms used in this study

Operator Availability	Number of available operators in a shift over the minimum number of operators needed to cover the average demand of labor hour in a perfectly lean system
Reagent Availability	Amount of reagent available to purchase in an order over the average demand of reagent in a perfectly lean system
Adverse Outcome Rate	Number of deceased patients or patients who have progressed beyond the capability of the treatment during the manufacturing process over the total number of patients received
Availability Threshold	Adverse outcome rate starts to rise when operator/reagent availability drops below the availability threshold
Base Stock	Reagents are replenished up to the base stock amount during each procurement order
Safety Factor	A factor that determines the amount of safety stock to prepare for uncertainty in demand
FIFO System	A first-in-first-out system where patients orders are processed based on the order of arrivals
PQ System	Priority queueing system when the sickest patients are moved to the front of the queue over regular patients

5.3 Results

This study analyzed how a sudden reduction in the available number of operators and a restriction in the amount of reagent supply available impacts the manufacturing process and how a delay in beginning therapy manufacturing can affect patient benefits. This simulation study assumes the manufacturing process is only initiated when there is sufficient reagent supply, available operators, and other equipment and resources to carry the process from beginning to finish. There will be no delay or stoppage during the

manufacturing process once the process begins unless the patient becomes too sick to receive the treatment or deceased.

Based on the simulation experiments, an "s-curve" behavior is observed for patient adverse outcome rate as operator and reagent availability decreased, where patient adverse outcome rate is defined as the ratio of the number of people who either become too sick to receive the treatment or who passed away during the production. The patient adverse outcome rate stays relatively flat when operator and reagent availability starts to drop. After these availabilities are lowered to a certain threshold, the adverse outcome rate starts to increase rapidly and slows down as the availability drops close to 0. The longer the disruption lasts, the worse patient adverse outcome becomes (Figure 5.3).

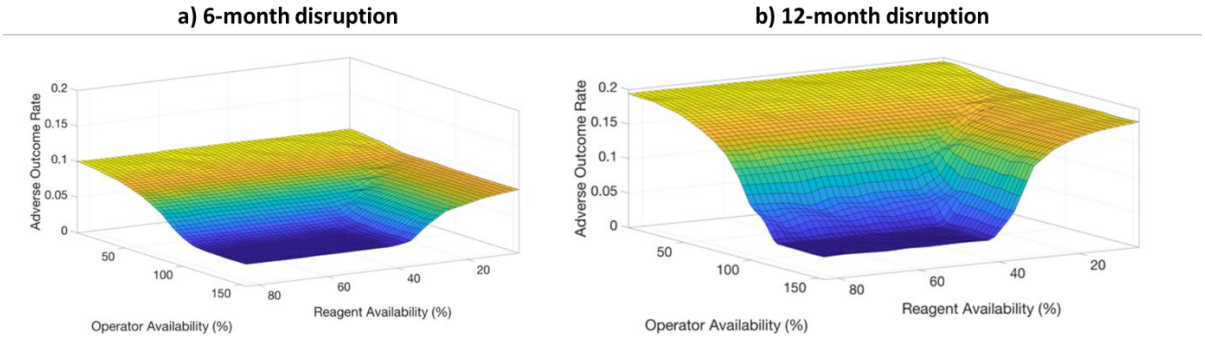

Figure 5.3 Response surface plots of patient adverse outcome rate versus reagent and operator availability for different disruption duration: 6 months (left) and 12 months (right) for a large factory with 5,000 orders per year

5.3.1 Operator disruption

To understand the impact of operator availability on patient adverse outcome rate, the study simulated scenarios where the number of operators was reduced during the disruption while the reagent supply remained adequate. As shown in Figure 5.4, the patient

adverse outcome rate starts to rise once operator availability drops below approximately 115%, above the theoretically minimum number of operators required. As the factory receives orders at random times, it is impossible for the operators to perfectly schedule unit operations that fill up 100% of their shift without gaps in between. Having the theoretically minimum number of operators per shift will cause production delay and an increase in adverse outcome rate. The availability threshold above which adverse outcome starts to rise appears to be consistent for factories of different sizes and disruption durations. A 12-month long disruption can more than double the adverse outcome rate to 0.21 from a 6-month disruption of 0.11. Larger factories seem to have a slightly worse increase in adverse outcomes compared to smaller factories. As the small factory (250 annual capacity) only requires a minimum of 4 people for 100% operator availability, it is not included in the analysis due to lack of sufficient data to display a clear trend.

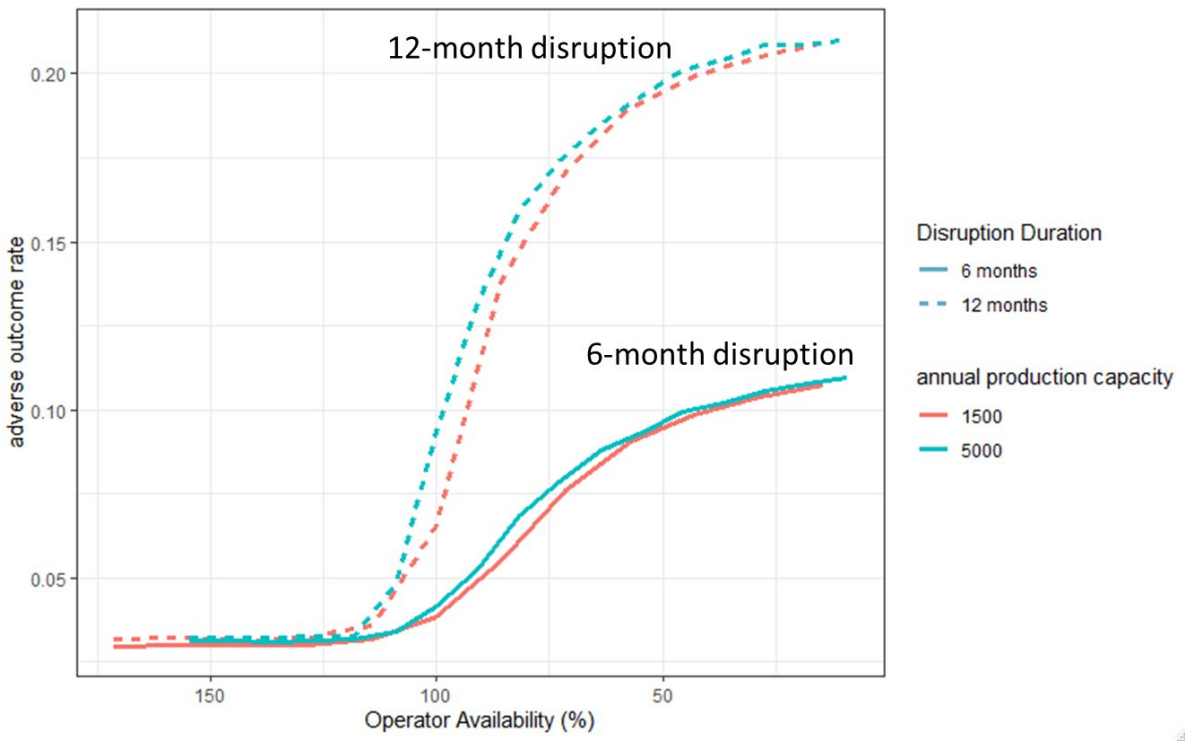

Figure 5.4 Impact of reduced operator availability during a disruption of different lengths on adverse outcomes on factories of different sizes. 100% operator availability is the minimum number of people required to cover the average labor hour demand in a shift

5.3.2 Reagent supply disruption

The study has investigated how different base stock levels, disruption durations, and different production capacities can impact patient adverse outcome rates when reagent supply becomes limited during the disruption period. When the disruption occurs, factories will have an upper limit on how much reagent they can order at a single decision epoch (e.g., once a week) and may no longer be able to order up to the base stock level. The safety factor, annual production capacities, and durations of disruption are listed in Table 5.7. The reagent availability threshold above which patient adverse outcome rate starts to rise are listed in Table 5.7 as well. The reduced delivery limit determines reagent availability

during the disruption over the average reagent demand during the same period. Unlike operator availability, the patient adverse outcome rate does not start to rise until reagent availability drops below 50% for all scenarios studied. The asymmetry arises because reagents can be stored while labor cannot. Factories will continue to receive new reagents at a reduced capacity, yet they will not be able to find replacements for absent operators during the disruption period.

Table 5.7 Reagent availability threshold for factories of different production capacities, of different safety factors for the base stock position, and the duration of disruptions

6 months				**12 months**			
Safety Factor / Annual Capacity	**0**	**3**	**6**		**0**	**3**	**6**
250	45.6%	45.6%	45.6%	**250**	45.6%	45.6%	45.6%
1,500	39.1%	39.1%	39.1%	**1,500**	39.1%	36.9%	41.3%
5,000	37.8%	37.8%	37.8%	**5,000**	39.1%	38.5%	38.5%

Similar to operator availability, a longer period of disruption leads to a higher patient adverse outcome rate (Figure 5.5). A year-long disruption can lead to a 19% patient adverse outcome rate, while a half-year-long disruption leads to a 7% patient adverse outcome rate. A lower safety factor for the base stock position will lead to a very small increase in patient adverse outcome rate (Figure 5.5a), although the safety factor does not appear to affect the availability threshold. On the other hand, larger factories have a lower availability threshold and can withstand a larger supply disruption without affecting the patient adverse outcome rate (Figure 5.5b). Larger factories have a lower adverse outcome

rate at a moderate level of disruption but will fare slightly worse than smaller factories when reagent availability becomes too low.

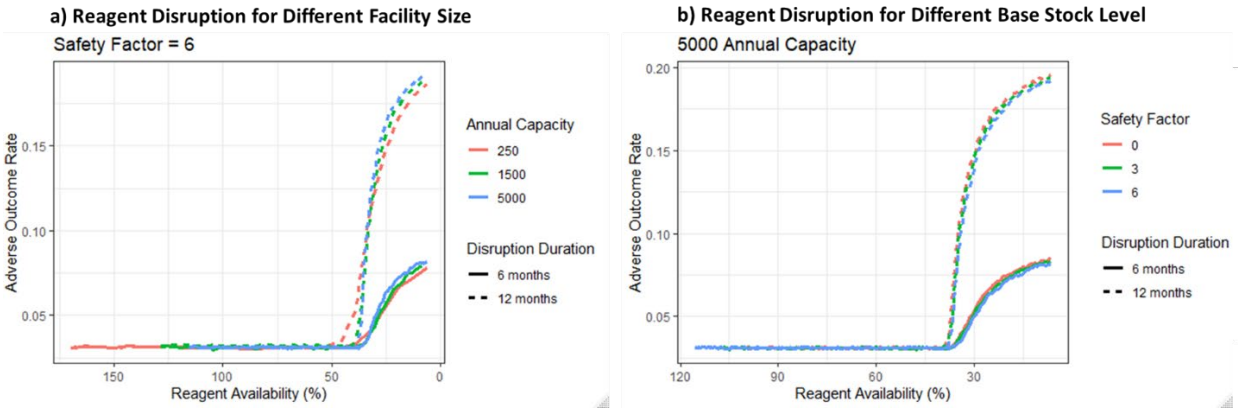

Figure 5.5 Patient adverse outcome rate vs. reagent availability with a) different base stock safety factor and disruption duration for a 5,000 annual capacity factory; b) different annual capacity and disruption duration for a base stock position with a safety factor of 6. 100% reagent availability means reagent delivery capacity equals the average demand of reagent in a perfectly lean system

5.3.3 Priority queueing policy

Implementing a priority queueing (PQ) policy has a modest effect in reducing the patient adverse outcome rate when operator availability is low, but the effect is almost negligible for reagent disruption (Figure 5.6a). The priority queueing policy has the largest impact at a moderate level of personnel disruption, reducing the patient adverse outcome rate by 7% when operators are reduced to 60% availability (Figure 5.6b). This policy is less effective at a higher disruption level since all the orders are backed up due to a lack of production personnel.

Further analysis also indicates that PQ reduces overall adverse outcomes without negatively impact on other patients waiting for their therapies. The PQ policy sharply

decreases the patient adverse outcome rate for urgent patients by almost 24% during moderate operator disruption without negatively impacting the patient adverse outcome rate for other patients (Figure 5.6c, d).

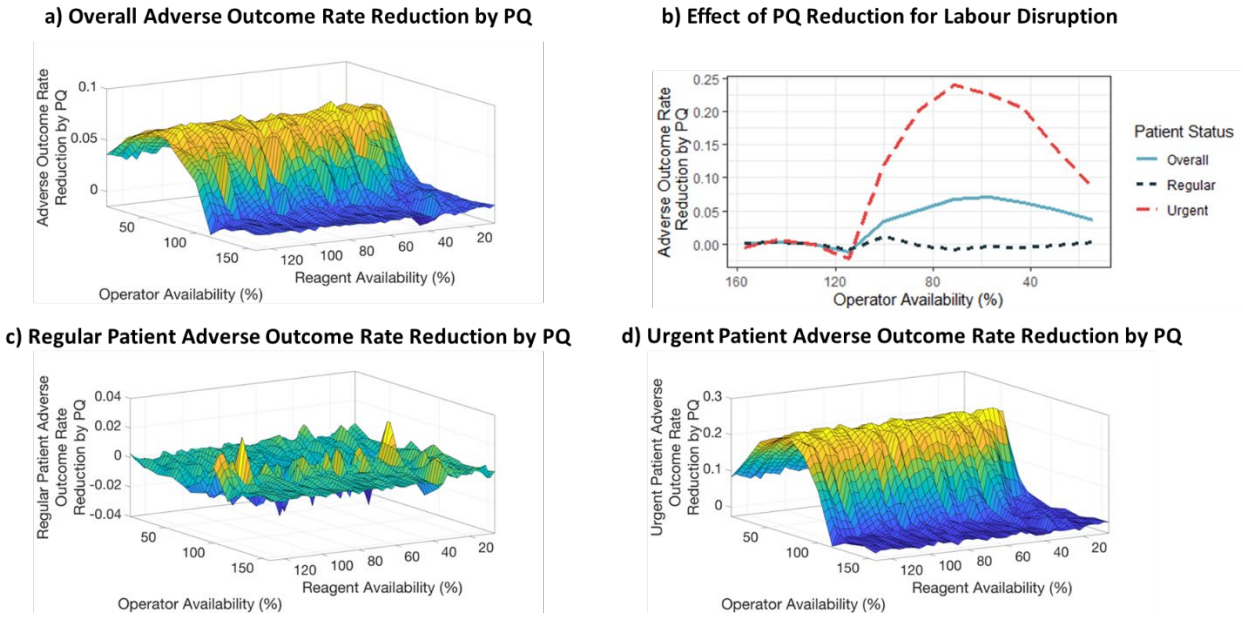

Figure 5.6 Impact of priority queueing policy on the patient adverse outcome. a) Overall adverse outcome reduction by priority policy. b) Adverse outcome reduction vs. operator availability. c) Regular patient adverse outcome reduction by PQ. d) urgent patient outcome reduction by PQ

5.4 Discussion

Simulation platforms can be effective tools for cell therapy manufacturers and cell processing facilities to conduct scenario planning, testing resilience, and making contingency plans for potential disruption events such as the COVID-19 pandemic. Having a simulation model of the actual manufacturing facility is especially helpful for complex and expensive manufacturing and supply chain system to estimate potential impacts

without the oversimplifications necessary for a pure analytical model to be tractable. However, foundational results derived from analytical models can be useful. For example, the simulation model described is much more computationally efficient. The reagent replenishment policy is assumed to be a base stock inventory policy, a policy known to be optimal for such inventory control problems, given a carefully chosen base stock level. The inputs to the model were based on published clinical trial data and communications with cell therapy manufacturers (Neelapu et al., 2017; Schuster et al., 2019). Manufacturers and cell processing facilities handling different cell types and with different facility configurations may obtain results that vary from those presented above using the simulation platform. The current model does not consider the cost-effectiveness of building redundancies into the manufacturing system and assumes the reagent and operator shortages remain constant during the length of the disruption. Future model development will incorporate cost information to understand the trade-offs between the cost of goods and system resilience to reach a setup that balances cost and risk. A decision support tool can also be developed to advise manufacturers on the optimal facility configuration to respond to the changing level of disruption severity in real-time.

Based on the simulation findings, cell therapy manufacturers should prioritize protecting key manufacturing personnel during the pandemic. Missing a few operators can significantly raise the patient adverse outcome rate. Hence, the facility manager should ensure that operators follow strict social distancing and other transmission prevention protocols as well as secure a sufficient supply of personal protective equipment (PPE) during the COVID-19 pandemic and future epidemics from emerging infectious diseases.

Facility managers should also be assured that a small amount of reagent supply reduction may only have a negligible impact on patients' benefit if facilities can still receive the limited supply on schedule. Establishing a second reagent supplier is also critical to maintaining the necessary manufacturing performance. In a hypothetical situation with two reagent suppliers, each supplying 50% of the reagent, a shutdown of one supplier will still allow the factory to have a reagent availability of 50%, above the ~40% threshold discovered in this study. In this scenario, having a second supplier will allow the factory to supply treatment to the patients without increasing the patient adverse outcome rate.

Larger factories appear to fare better than smaller factories faced with reagent disruption, but slightly worse with personnel shortage. A possible explanation is that smaller factories can be more efficient in reassigning the remaining workforce to cover the shift from absent operators, while larger factories have a larger safety stock compared to smaller factories to withstand a reagent shortage. It is also suspected that the impact of personnel shortage can also be influenced by the level of cross-training among the manufacturing personnel, which is not currently modeled in the simulation since smaller facilities are less likely to have reserves of people trained in specialized skills. These results may have further implications in understanding whether large, centralized manufacturing is more resilient than a network of smaller decentralized manufacturing facilities. The simulation model can be further utilized to study how a decentralized network of manufacturing facilities can be used to build overall system resilience and provide insight into facility design and space allocation for inventory areas.

The study has shown that priority queueing policies have the potential to significantly reduce the overall patient adverse outcome rate without negatively affecting

the patient adverse outcome rate of any subgroup of patients. The platform therefore can be a useful tool for manufacturers as well as policymakers, clinicians, and bioethicists to establish the criteria and conditions for priority access that maximize overall patient benefit. The simulation platform can be further developed to build a dynamic priority policy where the criteria for priority access or rationing can be automatically modified based on the availability of resources and severity of disruption in real-time. Such a tool would not only be beneficial to cell therapy developers but also for allocating vaccines, medicines in short supply, and ICU beds to manage COVID-19 and future pandemics from emerging infectious disease.

The utility of using a simulation tool to develop resilience in a manufacturing network will go beyond the COVID-19 pandemic. Even more than traditional pharmaceutical manufacturers, cell therapy developers will need to re-examine their inventory, equipment, and personnel policies and reorient the manufacturing and supply chain strategy from just-in-time and lean manufacture to a more robust and resilient approach that will save lives and reduce cost during serious disruptions.

5.5 Conclusions

This chapter has demonstrated the usefulness of an agent-based simulation platform to understand and develop resilience and risk mitigation strategies for cell therapy manufacturers. The study has shown that factories can tolerate reagent shortages better than labor shortages before the patient adverse outcome rate increases significantly. Consistent with intuition, longer disruptions are more difficult for factories to withstand and exact heavier tolls on patient benefit than shorter disruptions. The model suggests that manufacturing facilities with larger production capacities and a larger reagent safety stock

seems to have better patient outcomes during reagent shortages, while facilities with smaller production capacities tend to have better patient outcomes during labor shortages. Priority queueing policies can be effective in reducing the overall patient adverse outcome rate for a moderate level of operator disruption but has a negligible benefit for a severe level of operator disruption and appears to have no added benefit for reagent disruption.

Further studies can be conducted to analyze and develop resilience strategies for a network of manufacturing facilities and compare the resilience capability between centralized and decentralized manufacturing systems. A real-time decision support tool can also be developed to help manufacturers adjust operations in real-time to mitigate the impact of such disruptions once detected.

CHAPTER 6 CONCLUSIONS AND SUGGESTED FUTURE WORKS

6.1 Technological and fundamental knowledge contributions

This thesis describes a simulation-based decision support platform to help cell therapy manufacturers, including cell, gene, and tissue-engineered products, improve production and distribution. The platform can simulate a single or multi-network of manufacturing facilities throughout a large region. The platform incorporates a customized manufacturing process as each product is customized per patient and treats patients as part of the supply chain process before and after production. It takes into account reagent supply, temporal and individual variations of cell properties, demand surges, shortages of biological API, delivery location and timeframe, and other parameters for the manufacturing and supply chain process. The platform enables manufacturers to devise system-level decisions to improve facility design and predicts "what if" scenarios to plan for unexpected disruptions through the simulation of thousands of potential scenarios that may occur within the manufacturing and distribution of the cell therapy product. The simulations help manufacturers identify problems early on and throughout the overall manufacturing and supply chain, and could lead to reduced costs, improved yield, quality, and speed for the regenerative medicine products. Simulation case studies of different cell types (CAR-T, MSC, and iPSC) and different cell sources (autologous and allogeneic) are developed and presented. The thesis described multiple case studies that help stakeholders inform decision-making in cost reduction, automation, logistics, inventory management,

risk management, and scheduling with the possibility of adding more functions based on customers' demand.

In particular, **Chapter 1** and **Chapter 2** described why the agent-based simulation platform could be particularly suited to tackle fundamental challenges in cell therapy manufacturing and supply chain and described in detail the features and functionalities of the agent-based simulation platform. The chapters also outlined and listed the detailed manufacturing and supply chain requirement for different cell therapy products.

Chapter 3 and **Chapter 4** described the development and application of a cell therapy cost model that is capable of estimating and reducing manufacturing and distribution costs, as well as providing a platform for cost-effective facility design. The model enabled manufacturers to evaluate and choose appropriate technologies, reagents, equipment for the production process as well as compare different factory configurations to reduce manufacturing costs and improve yield. The model can also be extended to a network level to enable manufacturers to compare different distribution network strategies that minimize operating costs.

On a fundamental knowledge level, the thesis used the platform to identify all cost items within the cell therapy supply chain and established a methodology to categorize and analyze the cost based on transparency and variation among companies. A realistic manufacturing cost range was also established that serves as a benchmark for manufacturers to identify areas of cost reduction, and a list of potential cost reduction strategies for different cost categories was also provided.

Chapter 5 described the development of a scenario planning tool based on the simulation platform that can forecast the impact of supply chain disruption on

manufacturing facilities and analyzed the impact of different risk mitigation strategies. The platform can also provide decision support to determine the appropriate amount of resources needed to recover from supplier disruption and minimize the impact on patients.

On a fundamental knowledge level, the thesis used the platform to discover that patient adverse outcome displays an "s-curve" behavior with resource availability during disruption events, and impact to patients can be minimized if resource availability is kept above a certain threshold. The thesis established that a perfectly lean factory with no redundancy would not be able to recover from a disruption event, and having multiple suppliers can greatly reduce manufacturing delays. Additionally, implementing a priority queueing policy for urgent patients effectively reduces overall patient adverse outcome for reagent disruptions without negatively impacting regular patient outcome.

6.2 Current limitations and plan for further technology improvements

The technology described in the thesis is currently a NASA Technology Readiness Level (TRL) 4 prototype. The prototype has been tested and validated by academic and industrial collaborators within the NSF Engineering Research Center for Cell Manufacturing Technologies partnership. The technology has not yet been validated by a broad range of users or in an industrial environment for specific applications. More case studies and tests are still needed in a real-life environment to improve the functionality and optimize the design of the platform before the platform is ready for deployment in real industry settings. Some of the next steps to take for improving the platform include:

- Develop additional models for a wide range of regenerative medicine products beyond cell therapy to expand the broad applicability of the platform

- Generate support tools that help guide the manufacturer through various decision-making processes within the supply and manufacturing chain
- Refine the platform with an easy-to-use graphical user interface that can be widely deployed and interfaced with existing in-house database systems
- Test the platform within a real-world manufacturing facility to demonstrate that the system can provide meaningful and valuable insight to users of the technology
- Present the technology and supportive data to companies developing cell therapy products or those contract organizations specializing in manufacturing and distribution

6.3 Potential future research directions

This thesis will end with discussions of potential future directions of cell therapy manufacturing and propositions of future research topics.

6.3.1 Personalized manufacturing process for personalized cell therapy

Personalized medicine adapts medical decisions, practices, interventions, and products to the individual patient based on the patient's predicted response or risk of disease. The current simulation platform can be adapted to analyze the use and value of real-time patient and therapy data for personalized cell therapy manufacturing to enable new bio-manufacturing capabilities that do not exist today. The proposed research can address new modeling, analytic, and computational challenges to determine how to manufacture a cell therapy by adjusting the manufacturing and quality control processes in real-time, based on the current state of the patient's health and the current state of the therapy-in-process, in order to maximize clinical outcome at the time of therapy transfusion.

These results then set the stage to determine: (i) the order of patients waiting for therapy manufacturing to begin, based on current patient data for these patients, to maximize average clinical outcome at the time of therapy transfusion without reducing the clinical outcome of any patient in the wait queue and (ii) the best level of manufacturing capacity and the best reagent replenishment policy at a single manufacturing facility, given real-time patient and therapy data for all patients with therapies-in-progress, in order to minimize capital bioreactor expenditure and reagent replenishment costs for a given patient service level. The facility-level results set the stage for understanding the impact of supplier disruptions and the need for supply chain resilience at a time when the industry is moving from clinical trials to commercialization.

6.3.2 AI-based decision support for patient-centric manufacturing

The cell therapy manufacturing process involves multiple stakeholders with different emphasis on key performance indicators as listed in Table 2.1. Insurers may prioritize lowering cell therapy price and cost, while healthcare providers tend to emphasize the timeliness and efficacy of the product. By integrating machine learning algorithms into the simulation platforms, policymakers can explore and evaluate a set of reward and penalty policies that encourage the stakeholders, including manufacturers, payers, and care providers, to think from the patient’s perspective and prioritize patient outcome over other metrics.

The machine learning algorithms developed for the simulation platform will then be able to assist and automate many of the cell therapy manufacturing and supply chain decision-making process. For example, a reinforcement learning (RL) based job dispatcher algorithm can assign and schedule patients' orders to different manufacturing facilities and

automatically adapt to the complex and changing dynamics of the cell therapy supply chain. The RL-based dispatcher system has the potential to significantly improve the fulfillment rate and reduce delays over the intuition-based manual job dispatching process.

6.3.3 Intelligent cell therapy manufacturing with bio-cyber-physical system

The high manufacturing failure rate and difficulties to hit label specifications have driven many companies to deploy Industry 4.0 technologies to improve their processes. The current simulation platform can integrate with Industry 4.0 sensors, AI-driven real-time data analytics, and advanced process control capabilities to turn the manufacturing facility into a bio-cyber-physical system (BCPS) that fully integrates the physical agents within the facility with the virtual agents in the simulation platform. The computational core of the integrated system starts with an AI scenario learner that focuses on learning manufacturing patterns through a pattern recognition neural network. The recognized pattern will then be passed on to an AI system designer that uses generative network algorithms to continuously update the parameters within the virtual-physical integrated agents that leads to an improved production process. This integrated system will enable real-time predictions of final product quality at all manufacturing stages and create a more agile manufacturing process that automatically adapts to the manufacturing environment at any given time.

One particular application that is of great importance to the manufacturers is to use the system for preventative maintenance. Critical equipment in the facility can be equipped with connected and smart sensors that are connected to the platform. The platform will then be able to analyze equipment performances, predict the likelihood of equipment failures

and order preventative maintenance before the machines break down, reducing downtime and increasing production capabilities.

APPENDIX

Table A.01 List of CAR-T facilities used in Chapter 3 Case Study 3.

Name	City
Banner University of Arizona Medical Center/HCTT Program	Tucson, AZ
Phoenix Children's Hospital	Phoenix, AZ
UCSD Moores Cancer Center	La Jolla, CA
Lucile Packard Children's Hospital Stanford	Palo Alto, CA
Yale Cancer Center	New Haven, CT
Christiana Care Health Services, Inc	Newark, DE
Johns Hopkins All Children's Hospital	St. Petersburg, FL
Winship Cancer Institute of Emory University	Atlanta, GA
University of Chicago Medicine	Chicago, IL
Rush University Medical Center	Chicago, IL
Loyola University Medical Center	Maywood, IL
Holden Comprehensive Cancer Center at The University of Iowa	Iowa City, IA
The University of Kansas Cancer Center	Westwood, KS
University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center	Baltimore MD
Dana-Farber Boston Children's Cancer & Blood Disorders Center	Boston, MA
Beth Israel Deaconess Medical Center	Boston, MA
Barbara Ann Karmanos Cancer Institute	Detroit, MI
The Children's Mercy Hospital	Kansas City, MO
Roswell Park Comprehensive Cancer Center	Buffalo, NY
NewYork-Presbyterian / Columbia University Irving Medical Center	New York, NY
Cincinnati Children's Hospital Medical Center	Cincinnati, OH
University Hospitals Rainbow Babies & Children's	Cleveland, OH
Penn State Children's Hospital	Hershey, PA
Penn Medicine Abramson Cancer Center, Cell Therapy & Transplant Program	Philadelphia, PA
Fox Chase-Temple University Hospital Bone Marrow Transplant Program	Philadelphia, PA
Sarah Cannon Center for Blood Cancer at Tri Star Centennial	Nashville, TN
Texas Children's Hospital	Houston, TX
Children's Medical Center Dallas	Dallas, TX
Texas Transplant Institute at Methodist Hospital	San Antonio, TX
WVU Osborn Hematopoietic Malignancy and Transplantation Program	Morgantown, WV

Table A.02 Detailed material balances for reagents per batch in Chapter 4

From	To	Expansion Media (L)	Differentiation Media (L)	Formulation Media (L)	PBS (L)	TrypLE (L)	microcarrier (g)	DMSO (L)	solid reagent (g)	WFI (L)
Cold Bank	T75 Flasks									
T75 Flasks	0.1L Reactor	0.025								
0.1L Reactor	0.5L Reactor	0.12								
0.5L Reactor	3L Reactor	0.4								
3L Reactor	15L Reactor	2								
15L Reactor	80L Reactor	10								
80L Reactor	Centrifuge			5		7.853				
Centrifuge	MACS			0.3						
MACS	Vial Fill			1.31				0.28		
Media Prep	T75 Flasks	0.09								
Media Prep	0.1L Reactor	0.29					1.92			
Media Prep	0.5L Reactor	1.725					11.52			
Media Prep	3L Reactor	6.695					49.28			
Media Prep	15L Reactor	46.86					209.28			
Media Prep	80L Reactor	1757.15	100	5			1009.28			
Media Prep	Centrifuge			2.8						
Media Prep	MACS			1.28						
Reagent Storage	PBS Buffer Prep								2.5	25
PBS Buffer Prep	T75 Flasks				0.015					
PBS Buffer Prep	Centrifuge				25					
Trypsin Storage	T75 Flasks					0.003				
Trypsin Storage	0.1L Reactor					0.007				
Trypsin Storage	0.5L Reactor					0.044				
Trypsin Storage	3L Reactor					0.187				
Trypsin Storage	15L Reactor					1.211				
Trypsin Storage	80L Reactor					7.853				
Cold Bank	Quality Control	0.005								
T75 Flasks	Quality Control	0.005								
0.1L Reactor	Quality Control	0.005								
0.5L Reactor	Quality Control	0.005								

Table A.02 Continued

3L Reactor	Quality Control	0.005								
80L Reactor	Quality Control		0.005							
Centrifuge	Quality Control		0.005							
MACS	Quality Control		0.005							
T75 Flasks	Waste Treatment	0.07				0.003				
0.1L Reactor	Waste Treatment	0.19				0.007	1.92			
0.5L Reactor	Waste Treatment	1.49				0.044	11.52			
3L Reactor	Waste Treatment	5.09				0.187	49.28			
15L Reactor	Waste Treatment	38.86				1.211	209.28			
80L Reactor	Waste Treatment	1757.15	100			7.853	1009.28			
Centrifuge	Waste Treatment			7.5						
MACS	Waste Treatment			0.004				0.001		

Table A.03 List of equipment used in the allogeneic stem cell factory in Chapter 4, 1/2/3/4 in the unit column indicates the number of unit for year 1/2/3/4 and beyond

Vendor	Name	Unit	Description
VWR	Liquid nitrogen tank	2	Stores MSC seed vial
Astero	Cell thawing system	4	Thaw cells
Thermo Fisher	CO2 incubators	6	Supply CO2 and maintain temperature
PBS	MINI 0.1 Reactor	1/2/3/4	cell expansion
PBS	MINI 0.5 Reactor	1/2/3/4	cell expansion
PBS	MINI 3 Reactor	1/2/3/4	cell expansion
PBS	MINI 15 Reactor	1/2/3/4	cell expansion
PBS	MINI 80 Reactor	1/2/3/4	cell expansion and differentiation
kSep	Centrifuge	1/1/2/2	Isolate cells
Miotenyl Biotec	CliniMACS cell separation	1/1/2/2	Separate chondrocytes from MSC
Sartorius	Vial filling system	1/1/2/2	packaging and labeling
CryoMed	controlled rate freezer	1/1/2/2	freeze cell product
Thermo Fisher	Cryogenic storage	1/1/2/2	Store cell product
Thermo Fisher	Fridge/freezer	12	Reagent storage
Xcellerex	Quad mixing system	1/1/2/2	Heat up and pre-mix cell media
Tuttnauer	Industrial autoclave	4	Disinfect waste media and cells before disposal
NuAire	Biosafety cabinet	4	Quality control test
Extract	Cell therapy isolators	1/1/2/2	Provide an aseptic environment for cell manufacturing
Olympus	Microscope	4	Quality control test
Beckman Coulter	Multisizer	2	Cell count test
BioTEC	Plate Reader	2	Mycoplasma test
Endosafe	Endotoxin Test System	2	Test for endotoxin
Bio-Rad	qPCR	1	Identity test
Luna	Viable Cell Counter	1	Test for viability
Thermo Fisher	Hot Plate	1	quality control
Thermo Fisher	Rocker	4	quality control
Cole-Palmer	Ice Maker	1	miscellaneous

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VITA

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